WELLFLEET

Prior Authorization Guidelines

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Revised: 3/29/2021

PRIOR AUTHORIZATION POLICY

POLICY: Acthar Gel Prior Authorization Policy
- H.P. Acthar® Gel (repository corticotropin injection for intramuscular or subcutaneous use – Mallinckrodt)

REVIEW DATE: 03/25/2020; selected revision 12/16/2020

OVERVIEW

H.P. Acthar gel (Acthar), an adrenocorticotropic hormone (ACTH) analog, is indicated for the following uses:[1]

- **Infantile spasms** in infants and children less than 2 years of age.
- **Multiple sclerosis (MS) exacerbations** in adults.

Although data are limited, the prescribing information notes that Acthar may also be used for the following disorders and diseases:[1]

- **Allergic states**, such as serum sickness.
- **Collagen diseases**, during an exacerbation or as a maintenance therapy in selected cases of systemic lupus erythematosus and systemic dermatomyositis (polymyositis).
- **Dermatologic diseases**, such as severe erythema multiforme and Stevens-Johnson syndrome.
- **Edematous state** including to induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus.
- **Respiratory diseases** such as symptomatic sarcoidosis.
- **Rheumatoid disorders**, as an adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in psoriatic arthritis, rheumatoid arthritis (including juvenile rheumatoid arthritis) [selected cases may require low-dose maintenance therapy], and ankylosing spondylitis.
- **Ophthalmic diseases** including severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, and anterior segment inflammation.

Guidelines

Several guidelines discuss Acthar.

- **American Academy of Neurology and the Child Neurology Society** published an evidence-based guideline for the medical treatment of infantile spasms (2012).[2] ACTH is a first-line agent for the short-term treatment of infantile spasms.
- **Infantile Spasms Working Group** published a US consensus report on infantile spasms in 2010.[3] Most patients with this condition (90%) present within the first year of life. ACTH is an effective first-line therapy for infantile spasms.
- **Kidney Disease Improving Global Outcomes (KDIGO)** published clinical practice guidelines for glomerulonephritis (2012).[6] Due to limited data, recommendations cannot be made regarding ACTH.
- **National MS Society** has recommendations regarding corticosteroids in the management of MS (2008).[4] High-dose corticosteroids are the accepted standard of care short-term. The most common regimen is 500 to 1,000 mg of intravenous methylprednisolone given daily for 3 to 5 days, with or without an oral steroid tapering regimen (most often prednisone) for 1 to 3 weeks. Acthar and high-dose intravenous methylprednisolone have been shown to possess similar efficacy in the management of MS relapses.[5]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Acthar. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Acthar as well as monitoring required for adverse events and efficacy, approval requires Acthar to be prescribed by or in consultation with a physician who specializes in the conditions being treated. All denials will be forwarded to the Medical Director.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Acthar is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Infantile Spasms, Treatment.** Approve Acthar for 1 month if the patient meets the following criteria (A and B):
   A) Child is less than 2 years of age; AND
   B) Medication is prescribed by a physician who has consulted with or specializes in neurology.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Acthar is not recommended in the following situations:

1. **Multiple Sclerosis (MS) as "Pulse Therapy" on a Monthly Basis.** Preliminary data have investigated use of Acthar given as 80 units administered intramuscularly once a day for 3 days once a month.[7] This is not an accepted use of Acthar and more data are needed.

2. **Treatment of Proteinuria in Diabetic Nephropathy.** At this time, limited data are available[8] and Acthar is not established for this use.

3. **Treatment of Nephrotic Syndrome.** Very limited data have investigated the use of Acthar in patients with diagnoses including idiopathic membranous nephropathy, membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis, minimal change disease, immunoglobulin A nephropathy, class V SLE glomerulonephritis, monoclonal diffuse proliferative glomerulonephritis, and lupus nephritis.[9-25] Recommendations for use cannot be made at this time.

4. **Dermatomyositis or Polymyositis.** Data are limited in this clinical scenario[26,27] and controlled trials are needed before Acthar can be considered an established or recommended therapy.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
Selected Revision	Documentation is now required to confirm that the patient is treating an acute exacerbation of multiple sclerosis.	07/11/2018
Early Annual Revision	No criteria changes	07/25/2018
Early Annual Revision	The criteria regarding the treatment of acute exacerbations of multiple sclerosis in adults were removed. No recent quality data have emerged regarding this condition of use and other agents, such as intravenous methylprednisolone, are preferred in these clinical scenarios. Individual circumstances should be reviewed on a case-by-case basis, as needed.	04/10/2019 (effective 7/1/2019)
Selected Revision	The following criteria changes were made: 1. **Infantile Spasms, Treatment:** The criterion regarding age was changed from patients < 5 years of age to < 2 years of age. Regarding the requirement of a specialist, an epileptologist was removed from the criteria; the requirement that the medication be prescribed by or in consultation with a neurologist remains.	09/25/2019
Annual Revision	In the Policy Statement, wording was added that all reviews will be forwarded to the Medical Director.	03/25/2020 (effective 4/1/2020)
Update	08/26/2020: No criteria changes. The Policy Statement was change to reflect that all denials will be forwarded to the Medical Director. Previously all reviews were going to the medical director.	08/26/2020
Selected Revision	**Infantile Spasms – Treatment:** Criteria for specialist changed from "Acthar is prescribed by or in consultation with a neurologist" to "Medication is prescribed by a physician who has consulted with or specializes in neurology."	12/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Allergen Immunotherapy – Grass Pollen Sublingual Products Prior Authorization Policy

- Grastek® (Timothy grass pollen allergen extract sublingual tablets – ALK-Abello)
- Oralair® (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass mixed pollens allergen extract sublingual tablets – Stallergenes/Greer)

REVIEW DATE: 08/05/2020

OVERVIEW

Grastek and Oralair are grass pollen allergen extract sublingual tablets.[1,2] Grastek is a Timothy grass pollen allergen extract.[1] Oralair is a five-grass mixed pollen allergen extract.[2] Grastek and Oralair are indicated for:

- **Allergic rhinitis**, with or without conjunctivitis, that has been confirmed by a positive skin test or *in vitro* test for pollen-specific immunoglobulin E (IgE) antibodies for Timothy grass or cross reactive grass pollens (Grastek) or any of the five grasses contained in the product (Oralair). These products are indicated in patients 5 through 65 years of age.

Per product labeling, Grastek must be initiated 12 weeks before the expected onset of each grass pollen season and Oralair must be initiated 4 months before the expected onset of each grass pollen season.[1,2] Both must be continued throughout the season.

Clinical Efficacy

In clinical trials, therapy with the grass pollen sublingual immunoallergen agents prior to and during a single grass pollen season resulted in a 23% to 30% improvement in patients' Total Combined Score (TCS) [a

measurement of both allergic rhinitis with or without conjunctivitis symptoms and relief medication use] compared with placebo.[1,2] Longer-term data demonstrate a 38% to 40% improvement in the TCS with these agents vs. placebo.

Guidelines

Numerous guidelines address allergic rhinitis and allergen immunotherapy. In general, allergen immunotherapy should be considered for patients with allergic rhinitis or allergic asthma and an inadequate response to medical therapy who have evidence of specific IgE antibodies to clinically relevant allergens.[3,4] Grass pollen sublingual immunotherapy tablets are recommended for both short-term and long-term benefit in grass pollen-induced allergic rhinitis with or without conjunctivitis.[5,6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Grastek and Oralair. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Grastek and Oralair is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Grass Pollen-Induced Allergic Rhinitis.** Approve for 1 year if the patient meets ALL of the following criteria (A, B and C):
   - **A)** Patient is ≥ 5 years of age; AND
   - **B)** The timing of prescribing meets ONE of the following criteria (i or ii):
     - **i.** Grastek: Therapy is initiated 12 weeks prior to the expected onset of the grass pollen season or therapy is being dosed daily continuously for consecutive grass pollen seasons; OR
     - **ii.** Oralair: Therapy is initiated 4 months prior to the expected onset of the grass pollen season; AND
   - **C)** The diagnosis of grass pollen-induced allergic rhinitis is confirmed by meeting ONE of the following conditions (i or ii):
     - **i.** Patient has a positive skin test response to a grass pollen from the Pooideae subfamily of grasses (this includes, but is not limited to: sweet vernal, Kentucky blue grass, Timothy grass, orchard, or perennial rye grass); OR
     - **ii.** Patient has a positive *in vitro* test (i.e., a blood test) for allergen-specific immunoglobulin E (IgE) antibodies for a grass in the Pooideae subfamily of grasses (see examples above).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Grastek and Oralair is not recommended in the following situations:

6. **Concurrent Use of Grastek or Oralair with Subcutaneous Allergen Immunotherapy (e.g., Allergy Shots) or Sublingual Allergen Immunotherapy (e.g., Odactra™ [house dust mite {*Dermatophagoides farina* and *Dermatophagoides pteronyssinus*} allergen extract sublingual tablets], Ragwitek® [short ragweed pollen allergen extract sublingual tablets]).** The efficacy of Grastek and Oralair has not been evaluated in patients who are receiving concomitant allergen immunotherapy.[1] Approved product labeling for both Grastek and Oralair states that concomitant dosing with other allergen immunotherapy may increase the risk of local or systemic adverse events to

either subcutaneous or sublingual allergen immunotherapy. A Joint Practice Parameter specifically addressing sublingual immunotherapy (2017) highlights that no studies have evaluated the efficacy of multiple sublingual immunotherapy tablets administered together.[5] There is a need for further investigation to determine efficacy and optimal formulations for multi-allergen sublingual immunotherapy.

7. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	08/15/2018
Update	Date: 12/18/2018 Updated policy to reflect Oralair indication expanded down to 5 years of age. No change to approval criteria. Criteria previously approved and continues to approve for patients ≥ 5 years of age.	NA
Selected Revision	Removed the requirement that Grastek/Oralair be prescribed by or in consultation with an allergist, immunologist, or an otolaryngologist (ear, nose and throat [ENT]) physician specialist).	01/30/2019
Early Annual Revision	No criteria changes.	07/10/2019
Selected Revision	No criteria changes.	08/05/2020

PRIOR AUTHORIZATION POLICY

POLICY: Allergen Immunotherapy - Odactra Prior Authorization Policy

- Odactra™ (house dust mite [*Dermatophagoides farina* and *Dermatophagoides pteronyssinus*] allergen extract sublingual tablets – Merck)

REVIEW DATE: 08/05/2020

OVERVIEW

Odactra is a house dust mite allergen extract sublingual tablet indicated as immunotherapy for house dust mite-induced allergic rhinitis, with or without conjunctivitis, confirmed by *in vitro* testing for immunoglobulin E (IgE) antibodies to house dust mites or skin testing to licensed house dust mite allergen extracts.[1] It is approved for use in patients 18 to 65 years of age. Odactra is not indicated for the immediate relief of allergic symptoms.

Clinical Efficacy

In clinical trials involving adult patients (one pivotal study included a small number of pediatric patients), 52 weeks of therapy with Odactra resulted in a 17% to 18% improvement in patients' average Total Combined Rhinitis Score (TCRS) [a measurement of both rhinitis symptoms and relief medication use] compared with placebo.[2,3] In a 24-week environmental exposure chamber study, Odactra therapy resulted in a 48.6% improvement in the average total nasal symptom score (TNSS) compared with placebo.[4] There are limited data with Odactra in patients < 18 years of age as well; however, the safety and efficacy has not been established at this time.[5,6,13]

Guidelines

Several guidelines address allergic rhinitis with or without conjunctivitis, house dust mite allergy, and sublingual immunotherapy. In general, it is recommended that allergen immunotherapy should be considered for patients with allergic rhinitis or allergic asthma and an inadequate response to medical therapy who have evidence of specific IgE antibodies to clinically relevant allergens.[7,8,14] House dust mite sublingual allergen immunotherapy is recommended for long-term benefit in house dust mite-induced allergic rhinitis with or without conjunctivitis (in select guidelines).[9] There is more evidence supporting the use of subcutaneous immunotherapy and therefore, these agents are more widely recommended.[10] However, sublingual immunotherapy is noted to be safe and effective. Additionally, in patients with house-dust mite-driven allergic asthma, house dust mite sublingual immunotherapy tablets have demonstrated a robust effect on several critical asthma parameters (e.g., exacerbations, control, and safety) in adult patients.[11,12] Therefore, house dust mite sublingual immunotherapy is recommended as an add-on to standard asthma therapy in house dust mite-sensitized adults who continue to have asthma exacerbations despite standard therapy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Odactra. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Odactra is recommended in those who meet the following criteria:

FDA-Approved Indications

2. **House Dust Mite-Induced Allergic Rhinitis.** Approve for 1 year if the patient meets ALL of the following criteria (A and B):
   - **D)** Patient is ≥ 18 years of age; AND
   - **E)** The diagnosis of house dust mite-induced allergic rhinitis is confirmed by meeting ONE of the following conditions (i or ii):
     - **i.** Patient has a positive skin test response to house dust mite allergen extracts; OR
     - **ii.** Patient has a positive *in vitro* test (i.e., a blood test for allergen-specific IgE antibodies) for house dust mite.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Odactra is not recommended in the following situations:

8. **Concurrent Use of Odactra with Subcutaneous Allergen Immunotherapy (e.g., Allergy Shots) or Sublingual Allergen Immunotherapy (e.g., Grastek® [Timothy grass pollen allergen extract sublingual tablets], Oralair® [Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass mixed pollens allergen extract sublingual tablets], Ragwitek® [short ragweed pollen allergen extract sublingual tablets]).** The efficacy and safety of Odactra have not been evaluated in patients who are receiving concomitant allergen immunotherapy.[1] Approved product labeling for Odactra states that concomitant dosing with other allergen immunotherapy may increase the risk of local or systemic adverse events to either the subcutaneous or sublingual allergen immunotherapy.

9. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	06/13/2018
Selected Revision	Removed the requirement that Odactra be prescribed by or in consultation with an allergist, immunologist, or an otolaryngologist (ear, nose and throat [ENT]) physician specialist).	01/30/2019
Annual Revision	No criteria changes.	07/10/2019
Annual Revision	No criteria changes.	08/05/2020

PRIOR AUTHORIZATION POLICY

POLICY: Allergen Immunotherapy – Palforzia Prior Authorization Policy

- Palforzia® (peanut [*Arachis hypogaea*] allergen powder-dnfp for oral administration – Aimmune Therapeutics)

REVIEW DATE: 02/17/2021

OVERVIEW

Palforzia, an oral immunotherapy, is indicated for the **mitigation of allergic reactions**, including anaphylaxis, that may occur with accidental exposure to peanut.[1] It is approved for use in patients with a confirmed diagnosis of peanut allergy. Initial Dose Escalation may be administered to patients 4 through 17 years of age; Up-Dosing and Maintenance may be continued in patients ≥ 4 years of age. Palforzia is to be used in conjunction with a peanut-avoidant diet. It is not indicated for the emergency treatment of allergic reactions, including anaphylaxis. Prior to initiation, the prescriber should verify that the patient has injectable epinephrine and has been instructed on its appropriate use.

Clinical Efficacy

The Palforzia pivotal study, PALISADE (published) [n = 551 {n = 496 patients 4 to 17 years of age in the intent-to-treat (ITT) analysis}], included patients were required to have a diagnosis of peanut allergy supported by either a serum peanut-specific immunoglobulin E (psIgE) level of ≥ 0.35 allergen-specific unit per liter (kU_A/L) or a mean wheal diameter of at least 3 mm larger than the negative control to a skin-prick test (SPT) for peanut.[2] Additionally, to be eligible for randomization, patients had to have an allergic reaction (with dose-limiting symptoms) to a dose of 100 mg or less of peanut protein (equivalent to approximately one-third of a peanut kernel) during a double-blind, placebo-controlled food challenge (DBPCFC) at screening. Eligible patients were randomized (3:1) to receive either Palforzia or matching placebo administered once daily (QD). Following Initial dose Escalation, Up-Dosing, and 24 weeks of Maintenance Dosing, patients underwent an exit DBPCFC to assess their tolerance to peanut protein. In patients 4 to 17 years of age, 67.2% of patients receiving Palforzia (n = 250/372) were able to tolerate the single dose of 600 mg of peanut protein or more during the exit DBPCFC, compared with 4.0% (n = 5/124) with placebo (treatment difference: 63.2%; P < 0.001).

Guidelines

According to guidelines for the Diagnosis and Management of Food Allergy in the US from the National Institute of Allergy and Infectious Diseases (NIAID) expert panel (2010; 2017 addendum for the prevention of peanut allergy), medical history and a physical examination should guide the diagnosis, but parent and patient reports of food allergy must be confirmed, as 50% to 90% of patient-reported food allergies are not IgE-mediated food allergies.[4] An SPT and allergen-specific IgE testing are each recommended as a method to identify food that provoke allergic reactions. However, each test alone cannot be considered to be diagnostic for food allergy. The NIAID guidelines[3,4], as well as a Joint Task Force practice parameter on food allergy from the American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI)[5] and food allergy and anaphylaxis guidelines from the European Academy of Allergy and Immunology (EAACI) [2014][6] all recommend strict avoidance of peanut as the primary treatment for peanut allergy; anaphylaxis should be managed with epinephrine. These guidelines were published prior to the approval of Palforzia.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Palforzia. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Palforzia as well as the monitoring required for adverse events and long-

term efficacy, approval requires Palforzia to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Palforzia is recommended in those who meet the following criteria:

FDA-Approved Indication

3. Peanut Allergy. Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, D, E, and F):

F) Patient meets ONE of the following (i or ii):
- **i.** Patient is 4 to 17 years of age; OR
- **ii.** Patient is ≥ 18 years of age AND has been previously started on therapy with Palforzia prior to becoming 18 years of age; AND

G) Per the prescriber, the patient has a history of an allergic reaction to peanut that met each of the following (i, ii, and iii):
- **i.** Patient demonstrated signs and symptoms of a significant systemic allergic reaction; AND
  Note: Signs and symptoms of a significant systemic allergic reaction include hives, swelling, wheezing, hypotension, and gastrointestinal symptoms.
- **ii.** This reaction occurred within a short period of time following a known ingestion of peanut or peanut-containing food; AND
- **iii.** The prescriber deemed this reaction significant enough to require a prescription for an epinephrine auto-injector; AND
  Note: Examples of epinephrine auto-injectors include EpiPen, EpiPen Jr., Auvi-Q, and generic epinephrine auto-injectors.

H) Patient has a positive skin prick test (SPT) response to peanut with a wheal diameter ≥ 3 mm larger than the negative control; AND

I) Patient has a positive *in vitro* test (i.e., a blood test) for peanut-specific IgE (psIgE) with a level ≥ 0.35 kU_A/L; AND

J) Per the prescriber, Palforzia will be used in conjunction with a peanut-avoidant diet; AND

K) The medication is prescribed by or in consultation with an allergist or immunologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Palforzia is not recommended in the following situations:

10. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	02/12/2020
Annual Revision	No criteria changes.	02/17/2021

PRIOR AUTHORIZATION POLICY

POLICY: Allergen Immunotherapy – Ragwitek Prior Authorization Policy

- Ragwitek® (short ragweed pollen allergen extract sublingual tablets – ALK-Abello)

REVIEW DATE: 08/05/2020

OVERVIEW

Ragwitek is a ragweed pollen allergen extract sublingual tablet indicated as immunotherapy for the treatment of patients 18 to 65 years of age with short ragweed pollen-induced allergic rhinitis with or without conjunctivitis confirmed by a positive skin test or *in vitro* test for pollen-specific immunoglobulin E (IgE) antibodies for short ragweed pollen.[1] Ragwitek is not indicated for the immediate relief of allergy symptoms. Ragwitek is dosed once daily and must be initiated at least 12 weeks before the expected onset of ragweed pollen season and continued throughout the season.

Clinical Efficacy

Clinical trials enrolled adults with allergic rhinitis with or without conjunctivitis to have their diagnosis confirmed by a positive skin prick test and positive *in vitro* testing for serum IgE antibodies for short ragweed. In these patients, therapy with Ragwitek prior to and during the ragweed pollen season resulted in a 24% to 27% improvement in patients' Total Combined Score (a measurement of both allergic rhinitis with or without conjunctivitis symptoms and relief medication use) compared with placebo.[2,3] Ragwitek has also been evaluated in pediatric patients 5 to 17 years of age with allergic rhinitis with or without conjunctivitis; however, it is not indicated in this patient population.[1,8]

Guidelines

Numerous guidelines address allergic rhinitis and allergen immunotherapy. In general, allergen immunotherapy should be considered for patients with allergic rhinitis or allergic asthma and an inadequate response to medical therapy who have evidence of specific IgE antibodies to clinically relevant allergens.[4-7] FDA-approved sublingual immunotherapy agents, including Ragwitek, are recommended to be used only for the treatment of allergic rhinitis with or without conjunctivitis and not for other off-label conditions.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ragwitek. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ragwitek is recommended in those who meet the following criteria:

FDA-Approved Indications

4. Short Ragweed Pollen-Induced Allergic Rhinitis. Approve for 1 year if the patient meets ALL of the following criteria (A, B and C):
- **L)** Patient is ≥ 18 years of age;[1] AND
- **M)** Ragwitek therapy is initiated 12 weeks prior to the expected onset of the short ragweed pollen season; AND
- **N)** The diagnosis of short ragweed pollen-induced allergic rhinitis is confirmed by meeting ONE of the following conditions (i or ii):
  - **i.** Patient has a positive skin test response to short ragweed pollen; OR
  - **ii.** Patient has a positive *in vitro* test (i.e., a blood test) for allergen-specific immunoglobulin E (IgE) antibodies for short ragweed pollen.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ragwitek is not recommended in the following situations:

11. Concurrent Use of Ragwitek with Subcutaneous Allergen Immunotherapy (e.g., allergy shots) or Sublingual Allergen Immunotherapy (e.g., Grastek® [Timothy grass pollen allergen extract sublingual tablets], Oralair® [Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass mixed pollens allergen extract sublingual tablets], Odactra™ [house dust mite {*Dermatophagoides farina* and *Dermatophagoides pteronyssinus*} allergen extract sublingual tablets]). The efficacy of Ragwitek has not been evaluated in patients who are receiving concomitant allergen immunotherapy.[1] Approved product labeling for Ragwitek states that concomitant dosing with other allergen immunotherapy may increase the risk of local or systemic adverse events to either subcutaneous or sublingual allergen immunotherapy. A Joint Practice Parameter specifically addressing sublingual immunotherapy (2017) highlights that no studies have evaluated the efficacy of multiple sublingual immunotherapy tablets administered together.[8] There is a need for further investigation to determine efficacy and optimal formulations for multi-allergen sublingual immunotherapy.

12. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	08/15/2018
Selected Revision	Removed the requirement that Ragwitek be prescribed by or in consultation with an allergist, immunologist, or an otolaryngologist (ear, nose and throat [ENT]) physician specialist).	01/30/2019
Early Annual Revision	No criteria changes.	07/10/2019
Annual Revision	No criteria changes.	08/05/2020

PRIOR AUTHORIZATION POLICY

POLICY: Alpha$_1$-Proteinase Inhibitor Products Prior Authorization Policy

- Aralast NP™ (alpha$_1$-proteinase inhibitor [human] lyophilized powder – Shire)
- Glassia™ (alpha$_1$-proteinase inhibitor [human] solution – Shire)
- Prolastin®-C and Prolastin®-C Liquid (alpha$_1$-proteinase inhibitor [human] lyophilized powder and solution – Grifols Therapeutics)
- Zemaira® (alpha$_1$-proteinase inhibitor [human] lyophilized powder – CSL Behring)

REVIEW DATE: 10/21/2020

OVERVIEW

Alpha$_1$-proteinase inhibitor (also known as alpha$_1$-antitrypsin [AAT]), is indicated for use as a chronic augmentation and maintenance therapy in adults with alpha$_1$-proteinase deficiency and clinical evidence of emphysema.[1-5] The following products are available commercially in the US: Prolastin-C (also available as Prolastin-C Liquid), Aralast NP, Zemaira, and Glassia. The products vary in their availability and in some of their purification and viral inactivation processes.

Disease Overview

AAT deficiency is a rare, chronic, hereditary, autosomal co-dominant disorder marked by low concentrations of AAT which leads to progressive, severe emphysema that often does not manifest until the third to fourth decades of life.[1] One of the principal functions of AAT is the inhibition of neutrophil elastase, which is responsible for proteolytic degradation of matrix proteins.[6] When AAT is deficient, neutrophil elastase predominates and leads to breakdown of tissues, particularly in the parenchyma of the lungs. AAT can also predispose to liver disease since the protein is synthesized and can accumulate in hepatocytes. A large number of phenotypic variants exist, which have different clinical consequences.[6,7] This disease is most severe in those with null phenotypes (with no detectable circulating AAT in the plasma) or the PI*ZZ variant (AAT levels typically < 35% of normal).[1,7]

The goal of treatment is to increase AAT levels in the lungs to provide adequate anti-elastase activity. Treatment is aimed at raising serum levels of AAT above a theoretical protective threshold of 11 µM, which is equivalent to the tenth percentile of the AAT range of PI*SZ individuals; epidemiological data suggest lower probability of COPD above this level.[6] Of note, older laboratory techniques (e.g., radial immunodiffusion) measured non-purified levels of AAT, which tend to overestimate the concentration by 35% to 40%. To distinguish between non-purified and purified standards, the former are expressed in mg/dL and the latter are expressed in µM. An AAT level of 80 mg/dL measured by radial immunodiffusion corresponds to a plasma AAT level of 11 µM. Alpha$_1$-proteinase inhibitor is the only treatment approved

to correct AAT deficiency. The approved dosage regimen to achieve adequate concentrations in the lung is 60 mg/kg of body weight administered intravenously (IV) once weekly.

Guidelines

A European Respiratory Society (ERS) statement addresses diagnosis and treatment of pulmonary disease in alpha$_1$-antitrypsin deficiency (2017).[8] It is noted that augmentation therapy has been shown to reduce progression of emphysema in severe AATD deficiency. There is no evidence to support efficacy of AAT augmentation therapy for current smokers of any phenotype. These guidelines support earlier American Thoracic Society (ATS)/ERS guidelines (2003) which state that intravenous augmentation therapy is recommended for individuals with established airflow obstruction from AAT deficiency.[7]

The Canadian Thoracic Society updated its guidelines (2012) regarding AAT deficiency testing and augmentation therapy.[9] The guidelines state that evidence supports the consideration of AAT augmentation therapy in non-smoking or ex-smoking patients with COPD due to emphysema and a documented AAT deficiency (level $\leq$ 11 μmol/L). Patients should also be receiving other pharmacological and non-pharmacologic therapies, including comprehensive case management and pulmonary rehabilitation.

The Medical and Scientific Advisory Committee of the Alpha-1 Foundation guidelines (2016) provide similar recommendations.[10] Intravenous alpha$_1$-antitrypsin augmentation is strongly recommended in non-smoking or ex-smoking patients with forced expiratory volume (FEV_1) 30 to 65% of predicted due to well-documented benefit in this group. Weaker recommendations also support treatment of patients with FEV_1 below 30% of predicted or above 65% of predicted. Usual management of COPD should also be provided, with strong emphasis on facilitating tobacco cessation. Of note, AAT replacement therapy is not recommended for patients who continue to smoke.

Other Uses with Supportive Evidence

Although not indicated for this use, alpha$_1$-proteinase inhibitor therapy has been utilized for AAT-associated panniculitis, a rare complication characterized by erythematous nodules and plaques located on subcutaneous (skin) tissue in wide areas of the lower extremities, arms, trunk, and/or face.[11-16] The literature mainly documents case reports.[11-19] In the ATS/ERS 2003 guidelines, it is stated that AAT replacement therapy is a reasonable option for AAT deficiency-associated panniculitis.[7] Although no controlled trials provide a clear treatment recommendation, augmentation therapy with purified human alpha$_1$-proteinase inhibitor or fresh frozen plasma to restore plasma and local tissue levels of AAT appears to be rational, safe, and effective. In a review of treatment options for panniculitis in AAT deficiency, augmentation therapy with alpha$_1$-proteinase inhibitor was noted to be the most successful medical treatment.[20]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of alpha$_1$-proteinase inhibitor. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of alpha$_1$-proteinase inhibitor (e.g., Aralast NP, Glassia, Prolastin-C, Prolastin-C Liquid, Zemaira) is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Alpha$_1$-Antitrypsin Deficiency with Emphysema (or Chronic Obstructive Pulmonary Disease).** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has a baseline (pretreatment) AAT serum concentration of < 80 mg/dL or 11 μM (11 μmol/L); AND
   C) According to the prescriber, the patient is a current non-smoker.

Other Uses with Supportive Evidence

2. **Alpha$_1$-Antitrypsin Deficiency-Associated Panniculitis.** Approve for 1 year if the patient is ≥ 18 years of age.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of alpha1-proteinase inhibitor is not recommended in the following situations:

1. **Alpha$_1$-Antitrypsin Deficiency without Lung Disease, even if Deficiency-Induced Hepatic Disease is Present**. The ATS/ERS standards for the diagnosis and management of individuals with AAT deficiency (2003) state that the pathophysiology of liver disease in AAT deficiency is different from that of lung disease, and the use of alpha$_1$-proteinase inhibitor is not discussed for these patients.[7] There is an absence of information that suggests alpha$_1$-proteinase inhibitor is useful in patients with AAT deficiency-related liver disease.

2. **Bronchiectasis (without alpha$_1$-antitrypsin deficiency).** Studies have not demonstrated alpha$_1$ proteinase inhibitor to be effective for this condition. The ATS/ERS standards for the diagnosis and management of individuals with AAT deficiency (2003) state that despite the well-recognized association between AAT deficiency and the early development of emphysema, only a limited number of studies have assessed the association between AAT deficiency and bronchiectasis.[7] Studies suggest that bronchiectasis is more a result of emphysematous changes in the parenchyma than of AAT deficiency.

3. **Chronic Obstructive Pulmonary Disease (COPD) without Alpha$_1$-Antitrypsin Deficiency.** The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for the diagnosis, management, and prevention of COPD, updated in 2019, state that never or ex-smokers with an FEV_1 of 35 to 60% of predicted have been suggested as most suitable for AAT deficiency augmentation therapy; newer evidence suggests that individuals with higher FEV_1 values may also be candidates.[21] However, this therapy is not recommended for COPD that is unrelated to AAT deficiency.

4. **Cystic Fibrosis.** The use of alpha$_1$-proteinase inhibitor is considered investigational due to the lack of literature available regarding use of the agent for this disease state and many studies utilized an investigational aerosolized AAT delivery mechanism.[22-23]

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Approval duration decreased to 1 year from 3 years. Prolastin-C Liquid added to policy.	09/12/2018
Selected Revision	**Alpha$_1$-Antitrypsin Deficiency with Emphysema (or COPD):** Criteria added to require current non-smoking status for approval.	10/17/2018
Annual Revision	No criteria changes	10/09/2019
Annual Revision	**Alpha$_1$-Antitrypsin Deficiency with Emphysema (or Chronic Obstructive Pulmonary Disease):** A criterion was added to specify that the patient must be ≥ 18 years of age, in alignment with product labeling. **Alpha$_1$-Antitrypsin Deficiency-Associated Panniculitis:** A criterion was added requiring that the patient be ≥ 18 years of age.	10/21/2020

PRIOR AUTHORIZATION POLICY

POLICY: Amifampridine Products Prior Authorization Policy

- Firdapse® (amifampridine tablets – Catalyst Pharmaceuticals)
- Ruzurgi® (amifampridine tablets – Jacobus Pharmaceutical)

REVIEW DATE: 06/24/2020

OVERVIEW

Amifampridine is a broad spectrum potassium channel blocker.[1,2] The mechanism by which amifampridine exerts its therapeutic effect in patients with Lambert-Eaton myasthenic syndrome (LEMS) has not been fully elucidated.

- Firdapse is indicated for the treatment of LEMS in adults.[1]
- Ruzurgi is indicated for the treatment of LEMS in patients 6 years to < 17 years of age.[2]

Disease Overview

LEMS is a rare autoimmune disorder affecting the connection between nerves and muscles and causing proximal muscle weakness, autonomic dysfunction, and areflexia.[3,4] LEMS can occur at any age. The prevalence of LEMS specifically in pediatric patients is not known, but the overall prevalence of LEMS is estimated to be three per million individuals worldwide.[3] The characteristic weakness is thought to be caused by antibodies generated against the P/Q-type voltage-gated calcium channels (VGCC) present on presynaptic nerve terminals and by diminished release of acetylcholine (ACh).[4] More than half of LEMS cases are associated with small cell lung carcinoma (SCLC), which expresses functional VGCC. The diagnosis of LEMS is confirmed by electrodiagnostic studies, including repetitive nerve stimulation (RNS), or anti-P/Q-type VGCC antibody testing to confirm the diagnosis.

Clinical Efficacy

Firdapse was approved based on two pivotal trials.[1,5] One pivotal trial enrolled both amifampridine-naïve and treatment-experienced patients; patients were initially entered into an open-label run-in phase lasting 90 days.[5] During the open-label run-in phase, Firdapse was titrated for each individual patient to a dose that produced optimal neuromuscular benefit and tolerability in the opinion of the investigator. In order to continue in the study, treatment-naïve patients were required to have an improvement of at least three points in the quantitative myasthenia gravis score from the initial evaluation.

Although Ruzurgi is indicated for use in children, the efficacy of Ruzurgi for the treatment of LEMS was established in one randomized, double-blind, placebo-controlled, withdrawal study in adults with an established diagnosis of LEMS (n = 32).[2] Patients were required to be on an adequate and stable dosage for ≥ 3 months of Ruzurgi prior to entering the study. The efficacy of Ruzurgi in patients 6 to < 17 years of age is supported by evidence from adequate and well-controlled studies of Ruzurgi in adults with LEMS, pharmacokinetic data in adult patients, pharmacokinetic modeling and simulation to identify the dosing regimen in pediatric patients, and safety data from pediatric patients 6 to < 17 years of age.

Safety

Firdapse and Ruzurgi are contraindicated in patients with a history of seizures.[1,2] There is also a Warning/Precaution in the prescribing information for these medications because seizures have been observed in patients with and without a history of seizures taking amifampridine at the recommended doses. Many of these patients were taking medications or had comorbidities that may have lowered their seizure threshold. Seizures may be dose-dependent.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of amifampridine. Because of the specialized skills required for evaluation and diagnosis of patients treated with amifampridine as well as the monitoring required for adverse events and long-term efficacy, initial approval requires amifampridine to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of amifampridine is recommended in those who meet the following criteria:

FDA-Approved Indications

5. **Lambert-Eaton Myasthenic Syndrome (LEMS).** Approve amifampridine for the duration noted if the patient meets ONE of the following criteria (A or B):
   - **A)** Initial therapy. Approve amifampridine for 3 months if the patient meets the following criteria (i, ii, iii, and iv):
     - **i.** Patient is ≥ 6 years of age; AND
     - **ii.** Patient has confirmed LEMS based on at least one electrodiagnostic study (e.g., repetitive nerve stimulation) or anti-P/Q-type voltage-gated calcium channels antibody testing, according to the prescriber; AND
     - **iii.** Patient does not have a history of seizures; AND
     - **iv.** Amifampridine is being prescribed by or in consultation with a neurologist or a neuromuscular specialist; OR
   - **B)** Patient is Currently Receiving amifampridine. Approve amifampridine for 1 year if the patient is continuing to derive benefit from amifampridine, according to the prescriber.
     Note: Examples of continued benefit include improved muscle strength and improvements in mobility.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of amifampridine is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/09/2019
Annual revision	The policy name was changed from Firdapse PA to Amifampridine Products PA. Addition of Ruzurgi to the policy. The criterion restricting use to patients ≥ 18 years of age was changed to ≥ 6 years of age to reflect the age noted in Ruzurgi's indication.	06/18/2019
Annual revision	Prescribing physician was changed to prescriber throughout the criteria. No additional changes to criteria.	06/24/2020

PRIOR AUTHORIZATION POLICY

POLICY: Amyloidosis – Onpattro Utilization Review Medical Policy

- Onpattro® (patisiran intravenous injection – Alnylam)

REVIEW DATE: 10/28/2020

OVERVIEW

Onpattro, a lipid nanoparticle formulated RNA interference (RNAi) therapeutic, is indicated for treatment of adults with **polyneuropathy of hereditary amyloid transthyretin amyloidosis (hATTR)**.[1] hATTR is a rare, inherited, rapidly-progressive, debilitating, life-threatening disease.[2-4] It is a multisystem condition caused by mutation in the transthyretin (TTR) gene that results in misfolded TTR protein accumulation (as amyloid) in the nerves, heart, and other areas of the body. Onpattro targets hepatic production of mutant TTR. By reducing the unstable circulating TTR tetramers, organ deposition of amyloid is prevented, thus, stabilizing or improving symptoms of neuropathy.

Guidelines

There is a European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy (2016). Symptomatic management associated with sensory-motor neuropathy and autonomic dysfunction should be started at diagnosis.[3] This may include painkillers, antidiarrheal drugs, treatment of symptomatic orthostatic hypotension, diuretics for heart failure, prophylactic pacemaker implantation for conduction disorders, and/or vitrectomy/trabeculectomy for ocular amyloidosis or glaucoma. Tetramer stabilizers (tafamidis and diflunisal) are mentioned as treatment options that slow the rate of amyloidogenesis by preventing the dissociation, misfolding, and misassembly of mutated TTR. Tafamidis is recommended for use in patients with Stage 1 disease. Those presenting with Stage 2 disease are recommended for a clinical trial with an antisense oligonucleotide, small interfering RNA, doxycycline-tauroursodeoxycholic acid, or off-label use of diflunisal. For symptomatic relief of neuropathic pain due to hATTR, pregabalin, gabapentin, amitriptyline, and duloxetine are potential treatments.[5,6] Prior to the availability of drug therapies, liver transplantation (which removes the main source of mutated TTR) was the only treatment option for hATTR.[2]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Onpattro. All approvals are provided for the duration noted below. Because of the of the specialized skills required for evaluation and diagnosis of patients treated with Onpattro as well as the monitoring required for adverse events and long-term efficacy, approval requires Onpattro to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Onpattro is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis (hATTR).** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, E, and F):
   - **A)** Patient is ≥18 years of age; AND
   - **B)** Patient has a transthyretin (TTR) mutation as confirmed by genetic testing; AND
   - **C)** Patient has symptomatic polyneuropathy; AND
     Note: Examples of symptomatic polyneuropathy include reduced motor strength/coordination, and impaired sensation (e.g., pain, temperature, vibration, touch). Examples of assessments for symptomatic disease include history and clinical exam, electromyography, or nerve conduction velocity testing.
   - **D)** Patient has tried or is currently receiving at least one systemic agent for symptoms of polyneuropathy from one of the following pharmacologic classes: a gabapentin-type product, duloxetine, or a tricyclic antidepressant; AND
     Note: Examples of gabapentin-type products include gabapentin (Neurontin) and pregabalin (Lyrica). Examples of tricyclic antidepressants include amitriptyline and nortriptyline.
   - **E)** The patient does not have a history of liver transplantation; AND
   - **F)** The medication is prescribed by or in consultation with a neurologist, geneticist, or a physician who specializes in the treatment of amyloidosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Onpattro is not recommended in the following situations:

13. **Concomitant Use With Tegsedi (inotersen subcutaneous injection) or a Tafamidis Product.** Note: Examples of tafamidis products are Vyndaqel and Vyndamax. There are insufficient data supporting the safety and efficacy of concurrent use of these agents for ATTR-PN. The Vyndaqel/Vyndamax pivotal trial, which took place prior when Onpattro and Tegsedi were under investigation for amyloidosis, did not include patients who were taking investigational drugs. The pivotal trials for Onpattro and Tegsedi did not allow concurrent use of tetramer stabilizers (e.g., tafamidis, diflunisal). A Phase II open-label extension study (n = 27) included 13 patients who were treated concomitantly with Onpattro and tafamidis.[7] Following 24 months of treatment, there was no significant difference in the median serum TTR percent change from baseline with concomitant Onpattro and tafamidis (-80%) vs. Onpattro monotherapy (-88%).

14. Coverage is not recommended for circumstances *not* listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Onpattro lipid complex injection, for intravenous use [prescribing information]. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; February 2020.
2. Rizk M, Tüzmen Ş. Update on the clinical utility of an RNA interference-based treatment: focus on patisiran. *Pharmgenomics Pers Med*. 2017;10:267-278.
3. Adams D, Suhr OB, Hund E, et al. First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy. *Curr Opin Neurol*. 2016;29 Suppl 1:S14-26.
4. Gertz MA, Benson MD, Dyck PJ, et al. Diagnosis, prognosis, and therapy of transthyretin amyloidosis. *J Am Coll Cardiol.* 2015;66(21):2451-2466.
5. Ando Y, Coelho T, Berk JL. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare Dis*. 2013;8:31.
6. Kristen AV, Ajroud-Driss S, Conceição I, et al. Patisiran, an RNAi therapeutic for the treatment of hereditary transthyretin-mediated amyloidosis. *Neurodegener Dis Manag*. 2019;9(1):5-23.
7. Lin H, Merkel M, Hale C, Marantz JL. Experience of patisiran with transthyretin stabilizers in patients with hereditary transthyretin-mediated amyloidosis. *Neurodegener Dis Manag*. 2020;10(5):289-300.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis:** Add criteria to require patients to have tried or be currently taking a gabapentin-type product or a tricyclic antidepressant.	10/03/2018
Update	10/30/2018: For hereditary transthyretin-mediated amyloidosis, remove the word "documentation" from criterion that requires genetic testing for the transthyretin (TTR) gene mutation. This edit is intended to clarify that documentation is not required to be submitted for approval.	N/A
Annual Revision	**Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis:** The dose was clarified to be up to the maximum dose and shortest treatment interval. Duloxetine was added as a systemic agent that may be tried prior to Onpattro. **Conditions Not Recommended for Approval:** Concomitant use with Tegsedi or tafamidis products was added to the list of conditions not recommended for coverage.	10/16/2019
Annual Revision	**Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis:** To align with the approved labeling, criteria for symptomatic disease was reworded to require polyneuropathy (previously required peripheral neuropathy). Clinical exam, electromyography, or nerve conduction velocity testing were added as examples of assessments to confirm systematic disease. A criterion was also added to require that the patient does not have a history of liver transplantation.	10/28/2020

PRIOR AUTHORIZATION POLICY

POLICY: Amyloidosis – Tafamidis Products

- Vyndaqel (tafamidis meglumine capsules – Pfizer)
- Vyndamax (tafamidis capsules – Pfizer)

REVIEW DATE: 10/28/2020

OVERVIEW

Vyndaqel and Vyndamax, selective stabilizers of transthyretin (TTR), are indicated for the treatment of the **cardiomyopathy of wild-type or hereditary TTR-mediated amyloidosis** (ATTR-CM) in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization.[1] Studies excluded patients with New York Heart Association class IV disease.[2]

Disease Overview

In ATTR-CM, there is misfolding of the TTR protein resulting in accumulation of amyloid in the heart causing thickening of both ventricles.[2-6] ATTR-CM may be suspected following cardiac imaging (e.g., echocardiogram, cardiac magnetic imaging). Subsequent testing (e.g., scintigraphy or biopsy) confirms the diagnosis of ATTR-CM. Endomyocardial biopsy is almost 100% sensitive for diagnosis of transthyretin amyloidosis and is the gold standard for diagnosis. Biopsy can confirm if ATTR-CM is due to a hereditary mutant variant of TTR vs. an acquired wild-type variant. In patients with confirmed cardiac amyloidosis, TTR gene sequencing aids in treatment decisions and is necessary for genetic counseling in relatives of patients with a TTR variant. Although many mutations have been identified, mutation of V122I is the most common in the US. This mutation is present in 3% to 4% of African Americans and is associated with amyloid cardiomyopathy. Vyndaqel and Vyndamax bind to TTR at the thyroxine binding sites and stabilize the tetramer. This slows dissociation into monomers, which is the rate-limiting step in the amyloidogenic process.[1]

Guidelines

The Cleveland Clinic amyloidosis center has an update on the diagnosis and treatment of cardiac amyloidosis (2017), published prior to approval of Vyndaqel and Vyndamax in the US.[5] Treatment of

ATTR-CM focuses on management of cardiac symptoms and treating the underlying disease. Liver transplantation is a potential treatment for the hereditary mutant variant of TTR but not for wild-type disease. Heart transplantation (sometimes in combination with liver transplantation) is a treatment option for patients with both wild-type and hereditary variants of ATTR-CM. Although limited data are available, the following three pharmacologic classes were discussed for treatment or future treatment of the underlying ATTR-CM disease process: 1) agents that block TTR synthesis; 2) therapies that stabilize the TTR tetramer (e.g., tafamidis, diflunisal); and 3) agents that disrupt and clear the ATTR amyloid fibril (e.g., doxycycline).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of tafamidis products (Vyndaqel and Vyndamax). Because of the specialized skills required for evaluation and diagnosis of patients treated with Vyndaqel and Vyndamax as well as the monitoring required for adverse events and long-term efficacy, initial approval requires the agent to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vyndaqel and Vyndamax is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Cardiomyopathy of Wild-Type or Hereditary Transthyretin Amyloidosis.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is 18 years of age or older; AND
   - **B)** The diagnosis was confirmed by one of the following (i, ii, or iii):
     - **i.** A technetium pyrophosphate scan (i.e., nuclear scintigraphy); OR
     - **ii.** Amyloid deposits are identified on cardiac biopsy; OR
     - **iii.** Patient had genetic testing which, according to the prescriber, identified a transthyretin (TTR) mutation; AND
       Note: Examples of TTR mutations include Val122Ile mutation and Thr60Ala mutation. If the patient has wild-type amyloidosis, this is **not** a TTR mutation.
   - **C)** Diagnostic cardiac imaging has demonstrated cardiac involvement; AND
     Note: Examples of cardiac imaging include echocardiogram and cardiac magnetic imaging. Examples of cardiac involvement on imaging include increased thickness of the ventricular wall or interventricular septum.
   - **D)** Patient has heart failure, but does **not** have New York Heart Association class IV disease; AND
   - **E)** The medication is prescribed by or in consultation with a cardiologist or a physician who specializes in the treatment of amyloidosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tafamidis products (Vyndaqel and Vyndamax) is not recommended in the following situations:

15. **Concomitant Use With Onpattro (patisiran lipid complex intravenous infusion) or Tegsedi (inotersen subcutaneous injection).** There are no data supporting the safety and efficacy of concurrent use with Vyndaqel/Vyndamax. The Vyndaqel/Vyndamax pivotal trial, which took place

prior when Onpattro and Tegsedi were under investigation for amyloidosis, did not include patients who were taking investigational drugs. The pivotal trials for Onpattro and Tegsedi did not allow concurrent use of tetramer stabilizers (e.g., tafamidis, diflunisal). A Phase II open-label extension study, included 13 patients who were treated with concomitantly with Onpattro and tafamidis.[7] Following 24 months of treatment, there was not significant difference in the median serum TTR percent change from baseline with comcomitant Onpattro and tafamidis (-80%) vs. Onpattro monotherapy (-88%).

16. **Concurrent Use of Vyndaqel and Vyndamax.** There are no data available to support concomitant use.

17. **Polyneuropathy of Hereditary Transthyretin–Mediated Amyloidosis (hATTR)** [Note: For patients with hATTR and cardiomyopathy or mixed phenotype {concurrent cardiomyopathy and polyneuropathy}, refer to FDA-Approved Indication, above]. Neither Vndaqel nor Vyndamax are indicated for treatment of symptoms of polyneuropathy associated with hATTR.

18. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Vyndaqel and Vyndamax [prescribing information]. New York, NY: Pfizer; May 2019.
2. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2018;379(11):1007-1016.
3. Maurer MS, Elliott P, Merlini G, et al. Design and rationale of the Phase 3 ATTR-ACT clinical trial (tafamidis in transthyretin cardiomyopathy clinical trial). *Circ Heart Fail*. 2017;10(6).
4. Maurer MS, Bokhari S, Damy T, et al. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. *Circ Heart Fail.* 2019 Sep;12(9):e006075.
5. Donnelly JP, Hanna M. Cardiac amyloidosis: an update on diagnosis and treatment. *Cleve Clin J Med*. 2017;84(12 Suppl 3):12-26.
6. Siddiqi OK, Ruberg FL. Cardiac amyloidosis: an update on pathophysiology, diagnosis, and treatment. *Trends Cardiovasc Med*. 2018;28(1):10-21.
7. Lin H, Merkel M, Hale C, Marantz JL. Experience of patisiran with transthyretin stabilizers in patients with hereditary transthyretin-mediated amyloidosis. *Neurodegener Dis Manag*. 2020;10(5):289-300.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	05/15/2019
Early Annual Revision	**Cardiomyopathy of Wild-Type or Hereditary Transthyretin Amyloidosis:** Remove the requirement for genetic testing as a requirement. Add genetic testing as an alternative to nuclear scan or cardiac biopsy to confirm the diagnosis in patients with a TTR mutation (does not apply for patients with wild-type amyloidosis).	10/23/2019
Annual Revision	No criteria changes.	10/28/2020

PRIOR AUTHORIZATION POLICY

POLICY: Amyloidosis – Tegsedi Utilization Review Medical Policy

- Tegsedi® (inotersen injection for subcutaneous use – Ionis/Akcea Therapeutics)

REVIEW DATE: 10/28/2020

OVERVIEW

Tegsedi, an antisense oligonucleotide indicated for treatment of adults with **polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR)**.[1] hATTR is a rare, inherited, rapidly-progressive, debilitating, life-threatening disease.[2-3] It is a multisystem condition caused by mutation in the transthyretin (TTR) gene that results in misfolded TTR protein accumulation (as amyloid) in the nerves, heart, and other areas of the body. Tegsedi binds to TTR messenger RNA, causing degradation of mutant and wild-type TTR mRNA. This reduces serum TTR protein and TTR protein deposits in tissues.[1]

Guidelines

A European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy (2016) was published prior to approval of Tegsedi and Onpattro.[2] Symptomatic management associated with sensory-motor neuropathy and autonomic dysfunction should be started at diagnosis. This may include painkillers, antidiarrheal drugs, treatment of symptomatic orthostatic hypotension, diuretics for heart failure, prophylactic pacemaker implantation for conduction disorders, and/or vitrectomy/trabeculectomy for ocular amyloidosis or glaucoma. Tetramer stabilizers (tafamidis and diflunisal) are mentioned as treatment options that slow the rate of amyloidogenesis by preventing the dissociation, misfolding, and misassembly of mutated TTR. Tafamidis is recommended for use in patients with Stage 1 disease. Those presenting with Stage 2 disease are recommended for a clinical trial with an antisense oligonucleotide, small interfering RNA, doxycycline-tauroursodeoxycholic acid, or off-

label use of diflunisal. For the clinical symptoms associated with neuropathic pain due to hATTR, pregabalin, gabapentin, amitriptyline, and duloxetine are potential treatments.[5,6] Prior to the availability of drug therapies, liver transplantation (which removes the main source of mutated TTR) was the only treatment option for hATTR.[2]

Safety

Tegsedi has a Boxed Warning regarding sudden and unpredictable thrombocytopenia which may be life-threatening.[1] It is contraindicated in patients with a platelet count less than 100 x 10^9/L. Based on monitoring, Tegsedi may need to be interrupted or discontinued. Following discontinuation, continue to monitor platelet counts for 8 weeks (or longer if platelet count is less than 100 x 10^9/L). Tegsedi also has a Boxed Warning regarding glomerulonephritis, which may require immunosuppressive treatment and may lead to dialysis-dependent renal failure. Due to the risks and frequent monitoring for both serious bleeding caused by severe thrombocytopenia and because of glomerulonephritis, Tegsedi is only available through a restricted distribution program under the Tegsedi REMS (Risk Evaluation and Mitigation Strategy).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Tegsedi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tegsedi as well as the monitoring required for adverse events and long-term efficacy, approval requires Tegsedi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tegsedi is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Polyneuropathy of Hereditary Transthyretin–Mediated Amyloidosis (hATTR).** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, E, and F):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has a transthyretin (TTR) mutation as confirmed by genetic testing; AND
   - **C)** Patient has symptomatic polyneuropathy; AND
     Note: Examples of polyneuropathy include reduced motor strength/coordination, and impaired sensation (e.g., pain, temperature, vibration, touch). Examples of assessments for symptomatic disease include history and clinical exam, electromyography, or nerve conduction velocity testing.
   - **D)** Patient has tried or is currently receiving at least one systemic agent for symptoms of polyneuropathy from one of the following pharmacologic classes: a gabapentin-type product, duloxetine, or a tricyclic antidepressant; AND
     Note: Examples of gabapentin-type products include gabapentin (Neurontin) and pregabalin (Lyrica). Examples of tricyclic antidepressants include amitriptyline and nortriptyline.
   - **E)** Patient does not have a history of liver transplantation; AND
   - **F)** The medication is prescribed by or in consultation with a neurologist, geneticist, or a physician who specializes in the treatment of amyloidosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tegsedi is not recommended in the following situations:

19. **Concomitant Use With Onpattro (patisiran lipid complex intravenous infusion) or a Tafamidis Product.** Note: Examples of tafamidis products are Vyndaqel and Vyndamax. There are insufficient data supporting the safety and efficacy of concurrent use of these agents for ATTR-PN. The Vyndaqel/Vyndamax pivotal trial, which took place prior when Onpattro and Tegsedi were under investigation for amyloidosis, did not include patients who were taking investigational drugs. The pivotal trials for Onpattro and Tegsedi did not allow concurrent use of tetramer stabilizers (e.g., tafamidis, diflunisal). There is a Phase II open-label extension study (n = 27) using

Onpattro that included 13 patients who were treated concomitantly with tafamidis.[7] Following 24 months of treatment, there was no significant difference in the median serum TTR percent change from baseline with concomitant Onpattro and tafamidis (-80%) vs. Onpattro monotherapy (-88%).

20. Coverage is not recommended for circumstances *not* listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Tegsedi injection [prescribing information]. Carlsbad, CA: Ionis/Akcea Therapeutics; July 2020.
2. Adams D, Suhr OB, Hund E, et al. First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy. *Curr Opin Neurol*. 2016;29 Suppl 1:S14-26.
3. Gertz MA, Benson MD, Dyck PJ, et al. Diagnosis, prognosis, and therapy of transthyretin amyloidosis. *J Am Coll Cardiol*. 2015;66(21):2451-2466.
4. Onpattro injection [prescribing information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; September 2019.
5. Ando Y, Coelho T, Berk JL. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare Dis.* 2013;8:31.
6. Kristen AV, Ajroud-Driss S, Conceição I, et al. Patisiran, an RNAi therapeutic for the treatment of hereditary transthyretin-mediated amyloidosis. *Neurodegener Dis Manag*. 2019;9(1):5-23.
7. Lin H, Merkel M, Hale C, Marantz JL. Experience of patisiran with transthyretin stabilizers in patients with hereditary transthyretin-mediated amyloidosis. *Neurodegener Dis Manag*. 2020;10(5):289-300.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/10/2018
Update	10/30/2018: For hereditary transthyretin-mediated amyloidosis, remove the word "documentation" from criterion that requires genetic testing for the transthyretin (TTR) gene mutation. This edit is intended to clarify that documentation is not required to be submitted for approval.	N/A
Annual Revision	**Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis:** Duloxetine was added as a systemic agent that may be tried prior to Tegsedi. **Conditions Not Recommended for Approval:** Concomitant use with Onpattro or tafamidis products was added to the list of conditions not recommended for coverage.	10/16/2019
Annual Revision	**Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis:** To align with the approved labeling, criteria for symptomatic disease was reworded to require polyneuropathy (previously required peripheral neuropathy). Clinical exam, electromyography, or nerve conduction velocity testing were added as examples of assessments to confirm systematic disease. A criterion was also added to require that the patient does not have a history of liver transplantation.	10/28/2020

PRIOR AUTHORIZATION POLICY

POLICY: Antibiotics – Linezolid (Zyvox), Sivextro Prior Authorization Policy

- Linezolid tablets, oral suspension (Zyvox® – Pfizer, generics)
- Sivextro™ (tedizolid phosphate tablets – Cubist Pharmaceuticals)

REVIEW DATE: 10/14/2020

OVERVIEW

Linezolid (Zyvox) and Sivextro are synthetic oxazolidinone antimicrobial agents.[1-2] Both agents have clinical utility in the treatment of infections caused by aerobic Gram-positive bacteria. Cross-resistance between linezolid or Sivextro and other classes of antibiotics is unlikely because the mechanism of action for both of these agents differs from that of other antibacterial agents.

Linezolid is indicated in adults and children for the treatment of the following infections caused by susceptible strains of the designated microorganisms:[1]

- **Community-acquired pneumonia** (CAP), caused by *S. pneumoniae*, including cases with concurrent bacteremia, or *S. aureus* (MSSA only);
- **Complicated skin and skin structure infections** (cSSTIs), including diabetic foot infections, without concomitant osteomyelitis caused by *S. aureus* (MSSA and MRSA), *Streptococcus pyogenes,* or *Streptococcus agalactiae.* Zyvox has not been studied in the treatment of decubitus ulcers;
- **Nosocomial pneumonia**, caused by *Staphylococcus aureus* (methicillin-susceptible [MSSA] and methicillin-resistant strains [MRSA]), or *Streptococcus pneumoniae*;
- **Uncomplicated skin and skin structure infections** (SSTIs), caused by *S. aureus* (MSSA only) or *S. pyogenes*;
- **Vancomycin-resistant *Enterococcus faecium* (VRE) infections**, including cases with concurrent bacteremia.

Sivextro is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults and pediatric patients ≥ 12 years of age that are caused by susceptible isolates of the following Gram-positive microorganisms: *S. aureus* (MRSA and MSSA), *S. pyogenes*, *S. agalactiae*, *Streptococcus anginosus* Group (including *S. anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*), and *Enterococcus faecalis*.[2]

Although linezolid and Sivextro are indicated for susceptible strains of MSSA and drug-resistant strains of *S. pneumoniae* in some situations, it is not the optimal drug or drug of first-choice for these microorganisms.[3-4] Other antibiotics may be used. In efforts to reduce the development of drug-resistant bacteria and maintain effectiveness of linezolid and Sivextro, both antibiotics should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.[1,2] When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Guidelines

Diabetic Foot Infections

A clinical practice guideline for the diagnosis and treatment of diabetic foot infections (Infectious Diseases Society of America [IDSA] 2012) notes that diabetic foot infections of moderate severity may be treated with oral or initial parenteral therapy, while severe infections should be treated with parenteral therapy.[6] Linezolid, Cubicin® (daptomycin injection), and intravenous (IV) vancomycin are listed as therapy options for infections caused by MRSA (linezolid is the only oral therapy in this grouping).

Infective Endocarditis

Treatment guidelines, from the American Heart Association and endorsed by the IDSA (2015), recommend linezolid as a treatment option for patients with infective endocarditis caused by *Enterococcus* species that is resistant to penicillin, aminoglycosides, and vancomycin.[9]

MRSA

The 2011 IDSA guidelines for the treatment of MRSA infections recognize linezolid as a treatment option for other infections including infections of the central nervous system (e.g., meningitis, brain abscess), osteomyelitis, and septic arthritis.[5]

Pneumonia

Guidelines from the American Thoracic Society (ATS) and IDSA (2016) recommend that MRSA hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP) be treated with either vancomycin or linezolid rather than other antibiotics or other antibiotic combinations.[4] The choice between vancomycin and linezolid may be guided by patient-specific factors such as blood cell counts, concurrent prescriptions for serotonin-reuptake inhibitors, renal function, and cost. The available evidence indicates that vancomycin and linezolid are roughly similar and no alternative agent or regimen is clearly superior to these two products. Guidelines from the IDSA/ATS (2019) for CAP recommend vancomycin or linezolid for the treatment of community-acquired MRSA.[3] In addition, the Pediatric Infectious Disease Society and the IDSA guidelines (2011) for the treatment of CAP in infants and children > 3 months of age recommend linezolid as an alternative to vancomycin for treatment of MRSA, and as an alternative to ceftriaxone for the treatment of *S. pneumoniae* resistant to penicillin.[8]

Skin and Soft Tissue Infections (SSTIs)

According to the IDSA guidelines (2014) for the diagnosis and management of SSTIs, for mild nonpurulent (i.e., necrotizing infection, cellulitis, erysipelas) SSTI, oral antibiotics such as penicillin VK, cephalosporin, dicloxacillin, or clindamycin can be used.[7] For moderate nonpurulent SSTI, IV antibiotics such as penicillin, ceftriaxone, cefazolin, or clindamycin are recommended. For moderate purulent SSTIs, empiric treatment can be started with trimethoprim/sulfamethoxazole (TMP/SMX) or doxycycline. For MRSA infections, TMP/SMX is the recommended therapy. Cephalexin or dicloxacillin are usually effective for MSSA infections. For severe purulent SSTI, empiric therapy with IV vancomycin, Cubicin, linezolid, Vibativ® (telavancin powder for injection), or Teflaro® (ceftaroline powder for injection) are recommended. All of these agents are active against MRSA strains. For severe purulent SSTI caused by MSSA, therapy can be switched to nafcillin, cefazolin, or clindamycin.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of linezolid and Sivextro. All approvals are provided for the duration noted below. In cases where approval is in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

A. Coverage of linezolid is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Vancomycin-Resistant *Enterococcus* (VRE) Species Infection, Treatment**. Approve for 1 month.

2. **Methicillin-Resistant *Staphylococcus* Species Infection, Treatment**. Approve for 1 month.

Other Uses with Supportive Evidence

3. **Continuation of Linezolid Therapy.** Approve for 1 month in patients who meet ONE of the following criteria (a or b):
   - **a)** Patient is transitioning from intravenous (IV) linezolid or IV vancomycin to oral linezolid therapy; OR
   - **b)** Patient was started on oral linezolid in an inpatient facility and is continuing therapy.

4. **Treatment of an Infection that is Resistant to Other Antibiotics, but the Organism is Sensitive to Linezolid.** Approve for 1 month.

5. **There is Insufficient Information Available to Make a Determination Regarding Coverage and the Prescriber or Representative Cannot be Contacted.** Approve for up to 2 weeks of therapy.

   To avoid delays or disruption in therapy for the patient, if there is insufficient information available to make a determination regarding coverage and the prescriber or representative of the prescriber cannot be contacted, approve linezolid for up to 2 weeks.

B. Coverage of Sivextro is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Acute Bacterial Skin and Skin Structure Infections (ABSSSI) Caused by Methicillin-Resistant *Staphylococcus aureus* (MRSA), Selected *Streptococcus* Species (i.e., *Streptococcus pyogenes*, *Streptococcus agalactiae, Streptococcus anginosus* Group) and *Enterococcus faecalis*.** Approve for up to 6 days of therapy.

Other Uses with Supportive Evidence

2. **Continuation of Sivextro Therapy in the Outpatient Setting.** Approve for up to 6 days of therapy in patients transitioning from Sivextro IV therapy to oral therapy.

3. **There is Insufficient Information Available to Make a Determination Regarding Coverage and the Prescriber or Representative Cannot be Contacted.** Approve for up to 6 days of therapy.

   To avoid delays or disruption in therapy for the patient, if there is insufficient information available to make a determination regarding coverage and the prescriber or representative of the prescriber cannot be contacted, approve Sivextro. Since the available data for Sivextro only supports up to 6 days of therapy for the ABSSSI indication, we are limiting approval to this duration.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of linezolid and Sivextro is not recommended in the following situations:

21. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria for both linezolid and Sivextro. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	10/17/2018
Annual Revision	No criteria changes.	10/09/2019
Annual Revision	Changed prescribing physician to prescriber in the There is Insufficient Information Available to Make a Determination Regarding Coverage and the Prescriber Physician or Representative Cannot be Contacted criteria.	10/14/2020

PRIOR AUTHORIZATION POLICY

POLICY: Antibiotics – Synercid® (quinupristin and dalfopristin powder for injection – Pfizer)

DATE REVIEWED: 06/10/2020

OVERVIEW

Synercid is a combination of two streptogramin antibiotics, quinupristin and dalfopristin mixed in a 30:70 ratio.[1] Dalfopristin and quinupristin work synergistically in the bacterial ribosome where it inhibits early and late phase protein synthesis, respectively. Synercid is bactericidal against methicillin-susceptible and methicillin-resistant staphylococci.

Synercid is indicated in adults for the treatment of complicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible) or *Streptococcus pyogenes*.[1] To reduce the development of drug-resistant bacteria and maintain effectiveness of Synercid, it should only be used to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. Synercid should be continued for a minimum of 7 days for the treatment of complicated skin and skin structure infections.

Guidelines

Skin and Soft Tissue Infections (SSTIs)

According to the IDSA guidelines (2014) for the diagnosis and management of SSTIs, for mild nonpurulent (i.e., necrotizing infection, cellulitis, erysipelas) SSTI, oral antibiotics such as penicillin VK, cephalosporin, dicloxacillin, or clindamycin can be used.[2] For moderate nonpurulent SSTI, IV antibiotics such as penicillin, ceftriaxone, cefazolin, or clindamycin are recommended. For moderate purulent SSTIs, empiric treatment can be started with trimethoprim/sulfamethoxazole (TMP/SMX) or doxycycline. For methicillin-resistant *Staphylococcus aureus* (MRSA) infections, TMP/SMX is the recommended therapy. Cephalexin or dicloxacillin are usually effective for methicillin-susceptible *Staphylococcus aureus* (MSSA) infections. For severe purulent SSTI, empiric therapy with IV vancomycin, Cubicin, Zyvox, Vibativ® (telavancin powder for injection), or Teflaro® (ceftaroline powder for injection) are recommended. All of these agents are active against MRSA strains. For severe purulent SSTI caused by MSSA, therapy can be switched to nafcillin, cefazolin, or clindamycin. Synercid is recommended as an alternative in patients with severe penicillin hypersensitivity for the treatment of necrotizing infections of the skin, fascia, and muscle.

Other Uses With Supportive Evidence

In pooled data from two prospective, emergency-use studies conducted simultaneously, the safety and efficacy of Synercid was assessed in the treatment of patients (n = 396) with infections caused by vancomycin-resistant *Enterococcus faecium* infection and other gram-positive bacteria.[3] The most common types of infection were intra-abdominal, bacteremia, and urinary tract infections. Patients received Synercid 7.5 mg/kg intravenously (IV) once every 8 hours for a mean of 14.5 ± 10.7 days (range, 1 day to 108 days). The clinical success rate was 73.6% and the microbiologic success rate was 70.5% in the evaluable population. In another prospective, emergency-use study, the safety and efficacy of Synercid was assessed in the treatment of patients (n = 396) with infections caused by vancomycin-resistant *Enterococcus faecium* infection.[4] Bacteremia, intra-abdominal, and skin and skin-structure infections were the most common types of infection. Patients received Synercid 7.5 mg/kg IV every 8 hours for a mean of 13.7 ± 11 days. In the evaluable population, the clinical response rate was 68.8% and the microbiologic response rate was 68.0%. In an open-label trial, patients with nosocomial pneumonia caused by gram-positive bacteria were randomized to Synercid 7.5 mg/kg IV every 8 hours (n = 150) for a mean of 10.1 ± 4.0 days or vancomycin 1 gm every 12 hours (n = 148) for a mean of 9.5 ± 4.1 days.[5] In the bacteriologically evaluable group, clinical success was achieved by 56.3% of the patients receiving Synercid and in 58.3% of the patients receiving vancomycin (difference -2.0%; 95% confidence interval [CI]: -16.8%, 12.8%).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Synercid. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Synercid is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Skin and Skin Structure Infections, Complicated.** Approve for 1 month if the patient meets the following criteria (A and B):
   - **A)** The patient has an infection that is proven or strongly suspected to be caused by *Staphylococcus aureus* (methicillin-susceptible) or *Streptococcus pyogenes*; AND
   - **B)** The patient has severe penicillin hypersensitivity.

Other Uses with Supportive Evidence

2. **Treatment of an Infection Caused by a Microorganism that is Resistant to At Least Two Other Antibiotics, but the Organism is Sensitive to Synercid**. Approve for 1 month.

3. **Continuation of Synercid Therapy.** Approve for 1 month if the patient was started on Synercid and is continuing a course of therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Synercid has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

6. Synercid for injection [prescribing information]. New York, NY: Pfizer; July 2018.
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8. Moellering RC, Linden PK, Reinhardt J, et al. The efficacy and safety of quinupristin/dalfopristin for the treatment of infections caused by vancomycin-resistant *Enterococcus faecium*. *J Antimicrob Chemother*. 1999;44:251-261.
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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	06/12/2019
Annual Revision	No criteria changes.	06/10/2020

PRIOR AUTHORIZATION POLICY

POLICY: Antibiotics – Vancomycin Capsules Prior Authorization Policy

- Vancocin® (vancomycin capsules – Ani Pharmaceuticals; generics)

REVIEW DATE: 08/19/2020

OVERVIEW

Vancomycin capsules, an antimicrobial, are indicated for the treatment of *Clostridiodes difficile*- (formerly known as *Clostridium difficile)*-associated diarrhea and for the treatment of enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains).[1] The usual duration of therapy for the treatment of *C. difficile*-associated diarrhea in adults is 10 days and for pediatric patients, the duration is typically 7 to 10 days. The usual duration of therapy for the treatment of Staphylococcal enterocolitis in adults is 7 to 10 days.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of vancomycin capsules when being used in a compounded formulation for foot baths or other formulations co-formulated with one or more of the following: topical clindamycin products, topical clotrimazole products, topical ketoconazole products, and/or topical mupirocin products. All approvals are provided for the duration noted below.

Automation: This Prior Authorization policy will apply to vancomycin capsules when there is a prescription history of topical clindamycin products, topical clotrimazole products, topical ketoconazole products, and/or topical mupirocin products in the past 180 days. Prescriptions for vancomycin capsules without a claims history for topical clindamycin, topical clotrimazole, topical ketoconazole, and/or topical mupirocin products in the past 180 days are excluded from the Prior Authorization policy.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of vancomycin capsules is recommended in those who meet the following criteria:

FDA-Approved Indications

1. ***Clostridiodes Difficile* – Associated Diarrhea.** Approve for 2 weeks.

2. **Enterocolitis – Caused by *Staphylococcus aureus*.** Approve for 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of vancomycin capsules is not recommended in the following situations.

22. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

8. Vancomycin capsules [prescribing information]. Lake Forest, IL: Akorn, Inc.; August 2017.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/21/2019
Update	9/12/2019: Removed the formulations within the parentheses (Policy Statement and Automation): topical clindamycin products (gel, lotion,	NA

	solution), topical clotrimazole products (cream or solution), topical ketoconazole products (cream, foam, or gel), and topical mupirocin products (cream or ointment) such that the specific formulations are not listed. Revised wording: topical clindamycin products, topical clotrimazole products, topical ketoconazole products, and topical mupirocin products.	
Annual revision	No criteria changes.	08/19/2020

NA – Not applicable.

PRIOR AUTHORIZATION POLICY

POLICY: Antibiotics – Xifaxan Prior Authorization Policy

- Xifaxan® (rifaximin tablets – Salix Pharmaceuticals)

REVIEW DATE: 11/18/2020

OVERVIEW

Xifaxan, a rifamycin antibiotic, is indicated for the following uses:[1]

- **Hepatic encephalopathy**, to reduce the risk of overt disease in adults.
- **Irritable bowel syndrome (IBS) with diarrhea**, in adults.
- **Traveler's diarrhea**, caused by noninvasive *Escherichia coli* in patients ≥ 12 years of age.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Xifaxan and other antibacterial drugs, Xifaxan when used to treat infection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.[1] When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Limitations of Use: Xifaxan should not be used in patients with diarrhea complicated by fever or blood in the stool or diarrhea due to pathogens other than *E. coli*.[1]

Clinical Efficacy

The efficacy of Xifaxan for the treatment of small intestinal bacterial overgrowth (SIBO) was established in four clinical trials.[2-4] In two prospective, parallel-group trials, the efficacy of Xifaxan was assessed in 170 patients with a diagnosis of SIBO established with a glucose breath test (GBT).[2,3] Patients were randomized to rifaximin 600 mg/day, 800 mg/day, 1,200 mg/day, or 1,600 mg/day for 7 days. One month after treatment, the GBT normalization rate was 58% to 60% with 1,200 mg/day and 80% with 1,600 mg/day. In a clinical trial, 142 patients with SIBO were randomized to Xifaxan 1,200 mg/day or metronidazole 750 mg/day, both given for 7 days.[4] The GBT normalization rate, 1 month after treatment, was significantly higher with Xifaxan compared with metronidazole (63.4% vs. 43.7% odds ratio: 1.50; 95% confidence interval: 1.14, 4.38; $P < 0.05$). In a prospective trial, 50 consecutive children (mean age: 9.9 years; range: 3.2 to 15 years) with IBS were screened for SIBO.[5] There were 33 patients with SIBO and all patients were treated with rifaximin 600 mg/day for 7 days. Normalization of the lactulose breath test occurred in 64% of the patients with SIBO.

Guidelines

- **Hepatic Encephalopathy**: The American Association for the Study of Liver Diseases and the European Association for the Study of the Liver (AASLD/EASL) developed practice guidelines for the management of hepatic encephalopathy (2014).[6] The AASLD/ESLD guidelines state that Xifaxan add-on to lactulose is effective for the prevention of overt hepatic encephalopathy and for the prevention of recurrent episodes of hepatic encephalopathy after the second episode.
- **Irritable Bowel Syndrome with Diarrhea (IBS-D)**: The American College of Gastroenterology (ACG) guidelines for the management of IBS (2018) suggest Xifaxan to reduce the global symptoms of IBS and to reduce bloating in non-constipated IBS patients.[7] In addition, the

American Gastroenterological Association (AGA) guidelines on the management of IBS (2014) suggest Xifaxan over no drug treatment for patients with IBS-D.[8]

- **Small Intestine Bacterial Overgrowth:** Clinical guidelines from the ACG (2020) list Xifaxan 550 mg three times daily as a suggested antibiotic for the treatment of SIBO.[9] ACG also states that the diagnosis of SIBO can be made with breath testing (glucose hydrogen or lactulose hydrogen), or by small bowel aspiration and culture. In addition, practice guidelines from the AGA (2020) list Xifaxan 800 – 1,200 mg/day as an option for the treatment of SIBO.[10]
- **Travelers' Diarrhea**: The Centers for Disease Control and Prevention (CDC) Yellow Book – Health Information for International Travel (2020) state that Xifaxan may be used for the treatment of moderate, noninvasive travelers' diarrhea and may be used for the treatment of severe, nondysenteric travelers' diarrhea.[11] In addition, guidelines developed by an expert panel (2017) state that Xifaxan is appropriate for moderate or severe, nondysenteric travelers' diarrhea, and when indicated for the prophylaxis of travelers' diarrhea.[12]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Xifaxan. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indications

4. **Hepatic Encephalopathy.** Approve Xifaxan 550 mg tablets for 6 months if the patient meets the following criteria (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) According to the prescriber, the patient has previously had overt hepatic encephalopathy; AND
   C) Xifaxan will be used concomitantly with lactulose.

5. **Irritable Bowel Syndrome with Diarrhea.** Approve Xifaxan 550 mg tablets for 14 days if the patient is ≥ 18 years of age.

6. **Traveler's Diarrhea**. Approve Xifaxan 200 mg tablets for 3 days if the patient meets the following criteria (A, B, and C):
   A) Patient is ≥ 12 years of age; AND
   B) According to the prescriber, the patient is afebrile; AND
   C) According to the prescriber, the patient does not have blood in the stool.

Other Uses with Supportive Evidence

4. **Small Intestine Bacterial Overgrowth:** Approve Xifaxan (either strength) for 14 days if small intestine bacterial overgrowth is diagnosed by ONE of the following criteria (A, B or C):
   A) Glucose hydrogen breath test; OR
   B) Lactulose hydrogen breath test; OR
   C) Small bowel aspiration and culture.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xifaxan is not recommended in the following situations:

3. ***Helicobacter pylori* Infection**. There are limited data assessing the efficacy of Xifaxan in the treatment of *H. pylori* infection in adults.[7-9] The available studies are small, of poor quality, and none of the studies were conducted in the United States. In addition, treatment guidelines from the American College of Gastroenterology do not address the use of Xifaxan for the treatment of *H. pylori*.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	11/18/2020

PRIOR AUTHORIZATION POLICY

POLICY: Antibiotics (Inhaled) – Arikayce Prior Authorization Policy

- Arikayce® (amikacin liposome inhalation suspension for oral inhalation – Insmed)

REVIEW DATE: 10/28/2020

OVERVIEW

Arikayce is indicated for the treatment of ***Mycobacterium avium* complex (MAC) lung disease**, in adults who have limited or no alternative treatment options, as part of a combination antibacterial regimen in patients who do not achieve negative sputum cultures after at least six consecutive months of a background multidrug regimen (MDR) therapy.[1] As only limited clinical safety and efficacy data is available, reserve Arikayce for adults with limited or no other treatment options.

This indication is approved under accelerated approval based on achieving sputum culture conversion (defined as three consecutive negative monthly sputum cultures) by Month 6.[1]

Limitation of Use: Arikayce has only been studied in patients with refractory MAC lung disease defined as not achieving culture negativity after at least 6 months of background MDR treatment.[1] Arikayce is not recommended in patients with non-refractory MAC lung disease.

Disease Overview

Nontuberculous mycobacteria (NTM) are ubiquitous environmental microorganisms that are routinely found in soil and water, including both natural and treated water.[2-4] In susceptible people, NTM can cause pulmonary and extra-pulmonary disease.[2] MAC is by far, the most common NTM causing pulmonary nontuberculosis mycobacterial disease (PNTM) with *M. kansassii* and *M. abscessus* the second and third most common causes of PNTM.[2] The prevalence is higher in women than men,[2,3,5] and in the Southeast and the West.[3] The prevalence of PNTM increases with increasing age,[3] is associated with chronic obstructive pulmonary disease (COPD),[4] and 90% of the cases of PNTM occur in Caucasians, followed by Asians/Pacific Islanders and Blacks in the US.[3] Studies from North America have found the annual rate of isolation of NTM to range from 6 to 22 per 100,000 persons and the annual rate of PNTM to range from 5 to 10 per 100,000 persons.[5]

Treatment recommendations for MAC lung disease are based on disease severity and previous therapies received and almost all are three drug regimens.[6] For those with nodular/bronchiectatic disease or with fibrocavitary disease who cannot tolerate daily treatment, a three times weekly (TIW), three-drug regimen is recommended. The TIW regimen consists of azithromycin 500 to 600 mg or clarithromycin 1,000 mg, ethambutol 25 mg/kg, and rifampin 600 mg. For select patients with nodular/bronchiectatic disease (mild disease, medication intolerance, or goal of therapy is disease suppression), a two drug regimen consisting of azithromycin or clarithromycin plus ethambutol daily is acceptable. For patients with fibrocavitary disease or severe nodular/bronchiectatic disease, daily administration of azithromycin 250 to 300 mg or clarithromycin 500 to 1,000 mg, ethambutol 15 mg/kg, and rifampin 600 mg is recommended. Treatment recommendations for patients with severe or previously treated disease include azithromycin 250 to 300 mg or clarithromycin 500 to 1,000 mg, ethambutol 15 mg/kg, and rifabutin 150 to 300 mg or rifampin 600 mg daily. Intermittent IV amikacin or streptomycin are recommended for the first 2 to 3 months in patients with cavitary disease, or previous treatment failure. Patients should be treated for 12 months beyond the time that the sputum cultures convert to negative. For most patients conversion occurs within 6 months of initiation of treatment.

Guidelines

The American Thoracic Society (ATS), the European Respiratory Society (ERS), the European Society of Clinical Microbiology and Infectious Disease (ESCMID), and the Infectious Disease Society of America (IDSA) developed clinical practice guidelines for the treatment of nontuberculous mycobacterial pulmonary disease (2020 version).[6] The guidelines recommend the addition of liposomal amikacin to guideline-based therapy, in patients with MAC pulmonary disease who have failed treatment after ≥ 6 months of treatment with guideline-based therapy. Liposomal amikacin is not recommended for the initial treatment of MAC pulmonary disease.

The US Cystic Fibrosis Foundation and the European Cystic Fibrosis Society (2016 version) developed consensus recommendations on the treatment of NTM lung disease in which nebulized amikacin is listed as a treatment option for MAC and *M. abscessus* lung disease in cystic fibrosis (CF) patients.[7] The guidelines recommend that inhaled amikacin be used in conjunction with other NTM antibiotics.

Other Uses with Supportive Evidence

The efficacy of Arikayce in the treatment of *Pseudomonas aeruginosa* infection in CF patients has been assessed in three studies.[8] In a Phase III, randomized, open-label, non-inferiority study, 302 patients with CF were randomized to Arikayce 590 mg once daily (QD) or tobramycin inhalation solution (TIS) 300 mg twice daily. Patients received three cycles of treatment which consisted of 28 days on treatment followed by 28 days off treatment. The primary endpoint of the study was the relative change from baseline to the end of the 24-week study in forced expiratory volume in 1 second (FEV_1). Secondary endpoints included change in FEV_1 and forced expiratory volume % (FEV_1 %) predicted at various time points, change in CF Questionnaire-Revised (CFQ-R), time to first exacerbation, change in $\log_{10}$ colony-forming units (CFU), and all-cause hospitalization. The improvement in least squares mean FEV_1 at Day 168 was similar between Arikayce and TIS. The mean difference was -1.31% meeting the prespecified criteria for non-inferiority (lower bound of the 95% CI ≥ -5.0%). Change in FEV_1 at the end of each treatment course (Day

28, 84, and 140) and change in FEV_1 % predicted at the midpoint of cycle 1 (Day 14) and at the end of each treatment course were similar between treatment groups. More patients receiving Arikayce experienced pulmonary exacerbations compared with TIS; however, fewer patients required all-cause hospitalization. Change in CFQ-R was similar between groups at the end of each treatment course. Mean reductions in *P. aeruginosa* $\log_{10}$ CFU was similar for Arikayce and TIS at Day 28 and at Day 140.

A pooled report included 24 patients from two Phase Ib/IIa pharmacokinetic/pharmacodynamic studies with chronic *P. aeruginosa* infection.[9] Patients received liposomal amikacin 500 mg QD by inhalation for 14 days. Statistically significant changes from baseline to Days 7 and 14 were seen in FEV_1, FEV_1 % predicted, and forced expiratory flow between 25% and 75% of forced vital capacity. Another report included pooled data from two dose-ranging studies (one Phase Ib/IIa and one Phase IIa) in patients with CF (n = 105) chronically infected with *P. aeruginosa*.[9] Patients received 70, 140, 280 or 560 of liposomal amikacin or placebo QD for 28 days and followed for an additional 28 days. In repeated-measures mixed-effect models, the 560 mg dose was associated with statistically significant improvements in FEV_1, and FEV_1 % predicted and a reduction in $\log_{10}$ CFUs.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Arikayce. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Arikayce as well as the monitoring required for adverse events and long-term efficacy, approval requires Arikayce to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Arikayce is recommended in those who meet the following criteria:

FDA-Approved Indications

7. ***Mycobacterium avium* Complex (MAC) Lung Disease.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has NOT achieved negative sputum cultures for *Mycobacterium avium* complex within the past 3 months after completion of ≥ 6 consecutive months of a background multidrug regimen; AND
     Note: A multidrug regimen typically includes a macrolide (azithromycin or clarithromycin), ethambutol, and a rifamycin (rifampin or rifabutin).
   - **C)** Arikayce will be used in conjunction to a background multidrug regimen; AND
     Note: A multidrug regimen typically includes a macrolide (azithromycin or clarithromycin), ethambutol, and a rifamycin (rifampin or rifabutin).
   - **D)** The medication is prescribed by a pulmonologist, infectious diseases physician or a physician who specializes in the treatment of *Mycobacterium avium* complex lung infections.

Other Uses with Supportive Evidence

8. **Cystic Fibrosis**. Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient has *Pseudomonas aeruginosa* in culture of the airway (e.g., sputum culture, oropharyngeal culture, bronchoalveolar lavage culture); AND
   - **B)** The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Arikayce is not recommended in the following situations:

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/24/2018
Annual Revision	Removed cystic fibrosis from the list of Conditions Not Recommended for Approval and added it to Other Uses with Supportive Evidence.	10/23/2019
Selected Revision	*Mycobacterium avium* complex (MAC) lung disease: Added "within the past 3 months after completion of" to the criteria for sputum cultures.	06/24/2020
Annual Revision	No criteria changes.	10/28/2020

PRIOR AUTHORIZATION POLICY

POLICY: Antibiotics (Inhaled) – Cayston® (aztreonam inhalation solution – Gilead Sciences)

DATE REVIEWED: 04/08/2020

OVERVIEW

Cayston (aztreonam) is a monobactam antibiotic which inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins in susceptible organisms, including *Pseudomonas aeruginosa*, leading to cell death.[1] The presence of cystic fibrosis (CF) lung secretions does not reduce the activity of aztreonam.

Cayston is indicated to improve respiratory symptoms in CF patients with *P. aeruginosa*.[1] Safety and efficacy has not been established in pediatric patients below the age of 7 years, in patients with forced expiratory volume in 1 second (FEV_1) < 25% or > 75% predicted, or in patients colonized with *Burkholderia cepacia*.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cayston and other antibiotics, Cayston should be used to treat patients with CF known to have *P. aeruginosa* in the lungs.[1]

Disease Overview

CF is a complex, chronic, multi-organ, inherited disorder.[2] Lung disease accounts for nearly 85% of mortality in patients with CF. Lung destruction in CF is caused by obstruction of the airways due to dehydrated and thickened secretions, resultant endobronchial infection, and an exaggerated inflammatory response leading to development of bronchiectasis and progressive obstructive airway diseases. In patients with CF, there are a number of maintenance treatments that may be prescribed, including inhaled antibiotics.

Aerosolized delivery of antimicrobial agents for pulmonary infections provides an ideal method for achieving high local drug concentration in the lungs while minimizing systemic exposure.[3] It has been estimated that by 18 years of age, 80% of patients with CF have *P. aeruginosa* infection. Once *P. aeruginosa* is established in the respiratory tract of a patient with CF, the clinical course of the disease can worsen. Although many organisms can be found in the lower respiratory tract of patients who have CF, infection with mucoid *P. aeruginosa* is common and is associated with poorer outcomes.[4] Infection with chronic mucoid *P. aeruginosa* is associated with poor growth, more rapid decline in lung function, increased need for antibiotic treatment and hospitalization, and earlier death. In addition, mucoid *P. aeruginosa* (characterized by its biofilm) is more resistant to antibiotics than non-mucoid *P. aeruginosa*. Therefore, effective antimicrobial therapies targeting *P. aeruginosa* are central to the management of CF.

Clinical Efficacy

An open-label study assessed inhaled aztreonam for the eradication of newly acquired *P. aeruginosa* in children aged 3 months to < 18 years of age (n = 105).[5] In total, 49 patients < 6 years of age were included in the study. Patients received inhaled aztreonam 75 mg three times daily for 28 days. At the end of treatment with inhaled aztreonam, 91.5% of the patients (n = 43/47) < 6 years of age were culture-negative for *P. aeruginosa* and 76.6% of patients (n = 36/47) < 6 years of age remained culture-negative 4 weeks after completing the course of therapy.

Guidelines

The Cystic Fibrosis Foundation (CFF) established a Pulmonary Therapeutics Committee which provided recommendations, based on available evidence (2007) for the use of medications intended to maintain lung health.[2] In 2013 the Committee published updated recommendations for the use of chronic medications in the management of CF lung disease.[6] In patients ≥ 6 years of age with CF and moderate-to-severe lung disease with *P. aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled aztreonam is strongly recommended to improve lung function and quality of life (QoL). For mild disease, the Committee recommends chronic use of inhaled aztreonam for patients with CF ≥ 6 years of age with *P. aeruginosa* persistently present in cultures of the airways, to improve lung function and QoL.

The CFF published a systematic review of the literature regarding eradication of initial *P. aeruginosa* infections to develop guidelines for effective prevention (2014).[7] The recommendations pertaining to inhaled antibiotics are as follows: 1) Inhaled antibiotic therapy is recommended for the treatment of initial or new growth of *P. aeruginosa* (the favored antibiotic regimen is tobramycin [300 mg BID] for 28 days); and 2) Prophylactic antipseudomonal antibiotics to prevent the acquisition of *P. aeruginosa* are not recommended.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Cayston. All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Cayston as well as the monitoring required for adverse events and long-term efficacy, approval requires Cayston to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cayston is recommended in those who meet the following criteria:

FDA-Approved Indications

9. Cystic Fibrosis. Approve for 1 year if the patient meets the following criteria (A and B):
   A) The patient has *Pseudomonas aeruginosa* in culture of the airway (e.g., sputum culture, oropharyngeal culture, bronchoalveolar lavage culture); AND
   B) Cayston is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.

Other Uses with Supportive Evidence

10. Continuation of Cayston. Approve for 1 month if the patient was started on Cayston and is continuing course of therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Cayston has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

6. Nasal Rinse. Cayston is not approvable for compounding of aztreonam nasal rinse.

7. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/17/2019
Select revisions	**Cystic Fibrosis criteria.** Criteria requiring patient to be ≥ 6 years of age was removed. **Conditions Not Recommended for Approval**. Added compounded nasal rinse as a condition that is not approvable.	05/15/2019
Annual Revision	No criteria changes.	04/08/2020

PRIOR AUTHORIZATION POLICY

POLICY: Antibiotics (Inhaled) – TOBI® Podhaler (tobramycin inhalation powder – Novartis Pharmaceuticals)

DATE REVIEWED: 04/08/2020

OVERVIEW

Tobramycin is an aminoglycoside antibiotic which disrupts protein synthesis ultimately leading to cell death.[1] *In vitro,* tobramycin is bactericidal at concentration at or just above the minimum inhibitory concentration and has activity against gram-negative microorganisms including *Pseudomonas aeruginosa*.

TOBI Podhaler is indicated for the management of cystic fibrosis (CF) in patients with *P. aeruginosa*.[1] Safety and efficacy have not been demonstrated in patients < 6 years of age, patients with forced expiratory volume in 1 second (FEV1) < 25% or > 80% predicted, or patients colonized with *Burkholderia cepacia.*

Disease Overview

CF is a complex, chronic, multi-organ, inherited disorder.[2] Lung disease accounts for nearly 85% of mortality in patients with CF. Lung destruction in CF is caused by obstruction of the airways due to dehydrated and thickened secretions, resultant endobronchial infection, and an exaggerated inflammatory response leading to development of bronchiectasis and progressive obstructive airway diseases. In patients with CF, there are a number of maintenance treatments that may be prescribed, including inhaled antibiotics.

Aerosolized delivery of antimicrobial agents for pulmonary infections provides an ideal method for achieving high local drug concentration in the lungs while minimizing systemic exposure.[3] It has been estimated that by 18 years of age, 80% of patients with CF have *P. aeruginosa* infection. Once *P. aeruginosa* is established in the respiratory tract of a patient with CF, the clinical course of the disease can worsen. Although many organisms can be found in the lower respiratory tract of patients who have CF, infection with mucoid *P. aeruginosa* is common and is associated with poorer outcomes.[4] Infection with chronic mucoid *P. aeruginosa* is associated with poor growth, more rapid decline in lung function, increased need for antibiotic treatment and hospitalization, and earlier death. In addition, mucoid *P. aeruginosa* (characterized by its biofilm) is more resistant to antibiotics than non-mucoid *P. aeruginosa*. Therefore, effective antimicrobial therapies targeting *P. aeruginosa* are central to the management of CF.

Guidelines

The Cystic Fibrosis Foundation (CFF) established a Pulmonary Therapeutics Committee which provided recommendations, based on available evidence (2007) for the use of medications intended to maintain lung health.[2] In 2013 the Committee published updated recommendations for the use of chronic medications in the management of CF lung disease.[5] In patients ≥ 6 years of age with CF and moderate-to-severe lung disease with *P. aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled tobramycin is strongly recommended to improve lung function, quality of life, and reduce exacerbations. For mild disease, the Committee recommends chronic use of inhaled tobramycin for patients with CF ≥ 6 years of age with *P. aeruginosa* persistently present in cultures of the airways, to reduce exacerbations.

The CFF published a systematic review of the literature regarding eradication of initial *P. aeruginosa* infections to develop guidelines for effective prevention (2014).[6] The recommendations pertaining to inhaled antibiotics are as follows: 1) Inhaled antibiotic therapy is recommended for the treatment of initial or new growth of *P. aeruginosa* (the favored antibiotic regimen is tobramycin [300 mg BID] for 28 days); and 2) Prophylactic antipseudomonal antibiotics to prevent the acquisition of *P. aeruginosa* are not recommended.

The American Thoracic Society (ATS) published a clinical review (2013) of non-cystic fibrosis bronchiectasis on their webpage.[7] The review lists nebulized antibiotics (e.g., colistin, gentamicin, tobramycin) as treatment options for the eradication or suppression of *P. aeruginosa*. The European Respiratory Society (ERS) have published guidelines (2017) for the management of adult bronchiectasis and recommend patients with a new isolate of *P. aeruginosa* be offered eradication antibiotic treatment which includes nebulized antibiotics (e.g., colistin, gentamicin, tobramycin).[8] Neither the ATS or the ERS guidelines include Tobi Podhaler® (tobramycin inhalation powder) as a treatment option for bronchiectasis and no clinical trials have been published with Tobi Podhaler for treatment of non-cystic fibrosis bronchiectasis.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of TOBI Podhaler. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with TOBI Podhaler as well as the monitoring required for adverse events and long-term efficacy, approval requires TOBI Podhaler to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of TOBI Podhaler is recommended in those who meet the following criteria:

FDA-Approved Indications

11. Cystic Fibrosis. Approve for 1 year if the patient meets the following criteria (A, B and C):
- **A)** The patient is ≥ 6 years of age; AND
- **B)** The patient has *Pseudomonas aeruginosa* in culture of the airway (e.g., sputum culture, oropharyngeal culture, bronchoalveolar lavage culture); AND
- **C)** TOBI Podhaler is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.

Other Uses with Supportive Evidence

12. Continuation of TOBI Podhaler. Approve for 1 month if the patient was started on TOBI Podhaler and is continuing course of therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

TOBI Podhaler has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

8. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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44. Mogayzel PJ, Naureckas ET, Robinson KA, et al. Cystic Fibrosis Pulmonary Guidelines. Chronic Medications for Maintenance of Lung Health. *Am J Respir Crit Care Med*. 2013;187:680-689.
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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/17/2019
Annual Revision	No criteria changes.	04/08/2020

PRIOR AUTHORIZATION POLICY

POLICY: Antibiotics (Inhaled) – Tobramycin Inhalation Solution

- Bethkis® (tobramycin inhalation solution – Chiesi USA/Catalent Pharma Solutions)
- Kitabis™ (tobramycin inhalation solution – Catalent Pharma Solutions, authorized generic)
- TOBI® (tobramycin inhalation solution – Novartis Pharmaceuticals, generics)

DATE REVIEWED: 04/08/2020

OVERVIEW

Tobramycin is an aminoglycoside antibiotic which disrupts protein synthesis ultimately leading to cell death.[1] *In vitro*, tobramycin is bactericidal at concentration at or just above the minimum inhibitory concentration and has activity against gram-negative microorganisms including *Pseudomonas aeruginosa*.

TOBI and Kitabis are indicated for the management of cystic fibrosis (CF) in adults and pediatric patients ≥ 6 years of age with *P. aeruginosa*.[1,2] Safety and efficacy have not been demonstrated in patients < 6 years of age, patients with forced expiratory volume in 1 second (FEV1) < 25% or > 75% predicted, or patients colonized with *Burkholderia cepacia.*

Bethkis is indicated for the management of CF patients with *P. aeruginosa*.[3] Safety and efficacy have not been demonstrated in patients < six years of age, patients with FEV1 < 40% or > 80% predicted, or patients colonized with *B. cepacia*.

Disease Overview

CF is a complex, chronic, multi-organ, inherited disorder.[4] Lung disease accounts for nearly 85% of mortality in patients with CF. Lung destruction in CF is caused by obstruction of the airways due to dehydrated and thickened secretions, resultant endobronchial infection, and an exaggerated inflammatory response leading to development of bronchiectasis and progressive obstructive airway diseases. In patients with CF, there are a number of maintenance treatments that may be prescribed, including inhaled antibiotics.

Aerosolized delivery of antimicrobial agents for pulmonary infections provides an ideal method for achieving high local drug concentration in the lungs while minimizing systemic exposure.[5] It has been estimated that by 18 years of age, 80% of patients with CF have *P. aeruginosa* infection. Once *P. aeruginosa* is established in the respiratory tract of a patient with CF, the clinical course of the disease can worsen. Although many organisms can be found in the lower respiratory tract of patients who have CF, infection with mucoid *P. aeruginosa* is common and is associated with poorer outcomes.[6] Infection with chronic mucoid *P. aeruginosa* is associated with poor growth, more rapid decline in lung function, increased need for antibiotic treatment and hospitalization, and earlier death. In addition, mucoid *P. aeruginosa* (characterized by its biofilm) is more resistant to antibiotics than non-mucoid *P. aeruginosa*. Therefore, effective antimicrobial therapies targeting *P. aeruginosa* are central to the management of CF.

Guidelines

The Cystic Fibrosis Foundation (CFF) established a Pulmonary Therapeutics Committee which provided recommendations, based on available evidence (2007) for the use of medications intended to maintain lung health.[4] In 2013 the Committee published updated recommendations for the use of chronic medications in the management of CF lung disease.[7] In patients ≥ 6 years of age with CF and moderate-to-severe lung disease with *P. aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled tobramycin is strongly recommended to improve lung function, quality of life and reduce exacerbations. For mild disease, the Committee recommends chronic use of inhaled tobramycin for patients with CF ≥ 6 years of age with *P. aeruginosa* persistently present in cultures of the airways, to reduce exacerbations.

The CFF published a systematic review of the literature regarding eradication of initial *P. aeruginosa* infections to develop guidelines for effective prevention (2014).[8] The recommendations pertaining to inhaled antibiotics are as follows: 1) Inhaled antibiotic therapy is recommended for the treatment of initial or new growth of *P. aeruginosa* (the favored antibiotic regimen is tobramycin [300 mg BID] for 28 days); and 2) Prophylactic antipseudomonal antibiotics to prevent the acquisition of *P. aeruginosa* are not recommended.

Other Uses With Supportive Evidence

A few trials support the efficacy of tobramycin inhalation solution (TIS) for the treatment of bronchiectasis with *P. aeruginosa* infection. In a randomized, double-blind, placebo-controlled study, patients received either TIS 300 mg (n = 37) or placebo (n = 37) twice daily (BID) for 4 weeks and were followed for an additional 2 weeks off treatment.[9] At Week 4, the TIS group had a mean 4.54 $\log_{10}$ decrease in *P. aeruginosa* colony-forming units (CFU)/g of sputum compared with no change in the placebo group (P < 0.01). At Week 6, complete eradication of *P. aeruginosa* occurred in 35% of the patients in the TIS group compared with none in the placebo group, and 62% of patient in the TIS group vs. 38% of the placebo group had improvements in their general health (odds ratio 2.7; 95% confidence interval: 1.1, 6.9).

In a randomized, single-blind study, patients received TIS 300 mg (n = 16) or placebo (n = 19) BID for 3 months following a 14-day course of intravenous ceftazidime and tobramycin and were followed for an additional 12 months.[10] At the end of the study, 54.5% of the TIS group (n = 6/11) and 29.4% of the placebo group (n = 5/17) were free of *P. aeruginosa* (P = 0.048). In addition, patients in the TIS group had significantly fewer exacerbations (1.27 vs. 2.5; P = 0.044), hospital admissions (0.06 vs. 0.47; P = 0.037), and hospital days (0.9 vs. 13.56; P = 0.034) than the placebo group, respectively. No significant difference was found in pulmonary function tests.

A double-blind, placebo-controlled, crossover study randomized 30 patient to initial TIS 300 mg or placebo BID for 6 months, followed by a 1 month washout period and 6 months of therapy with the other treatment.[11] During the first treatment period, TIS treatment resulted in a significant reduction in *P. aeruginosa* density compared with placebo (P = 0.038). During both treatment periods, patients treated with TIS had fewer admissions (0.15 vs. 0.75; P = 0.038) and hospital days (2.05 vs. 12.65; P = 0.047) than patients treated with placebo, respectively. No significant changes occurred with number of exacerbations and pulmonary function tests.

In an open-label trial, 41 patients received three cycles of TIS 300 mg BID for 14 days followed by 14 days off therapy.[12] Patients were followed for an additional 40 weeks after the three cycles of treatment with TIS. At Week 10, there was a significant improvement from baseline (mean change 1.5 points; P = 0.006) in the composite pulmonary symptom score which included cough, shortness of breath, sputum production, fatigue, and wheezing. Quality of life, assessed using the St. George's Respiratory Questionnaire, was significantly improved at Week 10 (mean change 9.8; P < 0.001) compared with baseline. At Week 12, 22.2% of patients (n = 6/27) were considered to have *P. aeruginosa* eradicated from sputum cultures.

The American Thoracic Society (ATS) published a clinical review (2013) of non-cystic fibrosis bronchiectasis on their webpage.[13] The review lists nebulized antibiotics (e.g., colistin, gentamicin, tobramycin) as treatment options for the eradication or suppression of *P. aeruginosa*. The European Respiratory Society (ERS) have published guidelines (2017) for the management of adult bronchiectasis and recommend patients with a new isolate of *P. aeruginosa* be offered eradication antibiotic treatment which includes nebulized antibiotics (e.g., colistin, gentamicin, tobramycin).[14] While both the ATS and ERS list nebulized colistin and gentamicin as treatment options for non-cystic fibrosis bronchiectasis, neither drug has a commercially available formulation for nebulization.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of tobramycin inhalation solution. All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with tobramycin inhalation solution as well as the monitoring required for adverse events and long-term efficacy, approval requires tobramycin inhalation solution to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of tobramycin inhalation solution is recommended in those who meet the following criteria:

FDA-Approved Indications

13. Cystic Fibrosis. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** The patient has *Pseudomonas aeruginosa* in culture of the airway (e.g., sputum culture, oropharyngeal culture, bronchoalveolar lavage culture); AND
- **B)** Tobramycin inhalation solution is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.

Other Uses with Supportive Evidence

14. Bronchiectasis, Non-Cystic Fibrosis. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** The patient is ≥ 18 years of age; AND
- **B)** The patient has *Pseudomonas aeruginosa* in culture of the airway (e.g., sputum culture, oropharyngeal culture, bronchoalveolar lavage culture); AND
- **C)** Tobramycin inhalation solution is prescribed by or in consultation with a pulmonologist.

15. Continuation of Tobramycin Inhalation Solution Therapy. Approve for 1 month if the patient was started on tobramycin inhalation solution and is continuing course of therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Tobramycin inhalation solution has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

9. Nasal Rinse. Tobramycin inhalation solution is not approvable for compounding of tobramycin nasal rinse.

10. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/17/2019
Select revisions	**Cystic fibrosis**. Removed the age criteria for cystic fibrosis. **Conditions Not Recommended for Approval**. Added compounded nasal rinse as a condition that is not approvable.	05/15/2019
DEU update 06/26/2019	Added Kitabis authorized generic to the policy	Not applicable
Annual Revision	No criteria changes.	04/08/2020

PRIOR AUTHORIZATION POLICY

POLICY: Antibiotics (Injectable) Products Prior Authorization Policy

Generic	Brand	Manufacturer
Aminoglycosides		
Amikacin sulfate solution for injection		various
Gentamicin sulfate solution for injection		various
Plazomicin sulfate solution for injection	Zemdri™ (brand only)	Cipla USA, Inc
Streptomycin sulfate lyophilized powder for injection		various
Tobramycin sulfate solution for injection		various
Carbapenems		
Doripenem powder for injection		various

Generic	Brand	Manufacturer
Ertapenem sodium lyophilized powder for injection	Invanz®	Merck, others
Imipenem/cilastatin sodium powder for injection	Primaxin®	Merck, others
Meropenem powder for injection	Merrem®	Pfizer, others
Meropenem/vaborbactam powder for injection	Vabomere® (brand only)	Melinta Therapeutics, Inc
Cephalosporins		
Cefazolin sodium powder for injection		various
Cefotetan disodium powder for injection	Cefotan®	IGI Labs, Inc, others
Cefoxitin powder for injection		various
Cefuroxime sodium powder for injection		various
Cefotaxime sodium powder for injection	Claforan®	sanofi-aventis, others
Ceftazidime powder for injection	Tazicef®	Fortaz: various Tazicef: Hospira, others
Ceftriaxone powder for injection		various
Cefepime powder for injection	Maxipime™	various
Ceftaroline fosamil monoacetate powder for injection	Teflaro® (brand only)	Allergan
Ceftazidime/avibactam powder for injection	Avycaz® (brand only)	Allergan
Ceftolozane/tazobactam lyophilized powder for injection	Zerbaxa® (brand only)	Merck
Glycopeptides		
Dalbavacin hydrochloride powder for injection	Dalvance® (brand only)	Allergan
Oritavacin diphosphate lyophilized powder for injection	Orbactiv® (brand only)	Melinta Therapeutics, Inc
Telavacin hydrochloride lyophilized powder for injection	Vibativ® (brand only)	Theravance
Vancomycin hydrochloride lyophilized powder for injection		various
Lincosamides		
Clindamycin phosphate solution for injection	Cleocin phosphate®	Pharmacia & Upjohn, others
Lincomycin hydrochloride solution for injection	Lincocin®	Pharmacia & Upjohn, others
Macrolides		
Azithromycin lyophilized powder for injection	Zithromax®	Pfizer, others
Erythrocin lactobionate lyophilized powder for injection		various
Miscellaneous		
Aztreonam lyophilized powder for injection	Azactam®	Bristol-Myers Squibb, others
Colistimethate sodium powder for injection	Coly-Mycin® M	Par Pharmaceuticals, others
Daptomycin lyophilized powder for injection	Cubicin®	Merck, others
Metronidazole solution for injection		Various
Quinupristin/dalfopristin lyophilized powder for injection	Synercid® (brand only)	Pfizer
Sulfamethoxazole-trimethoprim solution for injection		various
Tigecycline lyophilized powder for injection	Tygacil®	Wyeth Pharmaceuticals, others
Oxazolidiones		
Linezolid solution for injection	Zyvox® (brand only)	Pharmacia & Upjohn, others
Tedizolid phosphate lyophilized powder for injection	Sivextro® (brand only)	Merck
Penicillins		
Ampicillin sodium powder for injection		various
Ampicillin sodium/sulbactam	Unasyn®	Pfizer, others
Nafcillin sodium powder for injection		various
Oxacillin sodium powder for injection		various
Penicillin G benzathine suspension for injection		various
Penicillin G procaine suspension for injection		various
Penicillin G potassium solution for injection		various
Penicillin G sodium powder for injection		various
Piperacillin sodium/tazobactam suspension for injection	Zosyn®	Wyeth Pharmaceuticals, others
Quinolones		
Ciprofloxacin solution for injection	Cipro® IV	Bayer, others
Delafloxacin meglumine suspension for injection	Baxdela® (brand only)	Melinta Therapeutics, Inc
Levofloxacin solution for injection		various
Moxifloxacin solution for injection	Avelox® IV	Bayer, others
Tetracyclines		
Eravacycline di-hydrochloride lyophilized powder for injection	Xerava (brand only)	Tetraphase Pharmaceuticals, Inc
Doxycycline hyclate lyophilized powder for injection	Doxy 100™	Fresenius Kabi, others
Minocycline hydrochloride powder for injection	Minocin® (brand only)	Melinta Therapeutics Inc

Generic	Brand	Manufacturer
Omadacycline tosylate lyophilized powder for injection	Nuzyra® (brand only)	Paratek Pharmaceuticals, Inc

REVIEW DATE: 08/19/2020

OVERVIEW

Injectable antibiotics are used to treat moderate to severe bacterial infections.[1] In addition, injectable antibiotics can also be used for prophylactic indications (e.g., before surgeries; in immunocompromised patients [e.g., patients with cancer]).

Recently, some injectable antibiotics are being used with nasal or nebulized corticosteroids to compound nasal rinses and nasal irrigations. There are no data to support the use of these products.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of the injectable antibiotics listed above, when these products are prescribed in conjunction with nasal or nebulized dosage forms of beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone, or triamcinolone. The list of injectable antibiotics in this policy is not inclusive; other injectable antibiotics may also be targeted in this edit. Approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: This Prior Authorization policy will apply to injectable antibiotics when there is a prescription history of a nasal or nebulized formulation of the selected corticosteroid (beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone, triamcinolone) in the past 180 days. Prescriptions for injectable antibiotics without a claims history for nasal or nebulized corticosteroids in the past 180 days are excluded from the Prior Authorization policy.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of injectable antibiotics is recommended in those who meet the following criteria:

FDA-Approved Indications

3. Systemic Bacterial Infections (Prophylaxis or Treatment). Approve for 3 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of injectable antibiotics is not recommended in the following situations:

23. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

9. Facts and Comparisons® Online. Wolters Kluwer Health, Inc.; 2020. Available at: http://online.factsandcomparisons.com/login.aspx?url=/index.aspx&qs=. Accessed on August 13, 2020. Search terms: aminoglycoside, carbapenem, cephalosporin, glycopeptide, lincosamide, macrolide, oxazolidione, penicillin, quinolone, tetracycline.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/07/2019
Update	08/20/2019: Policy name is changed from Antibiotics (Intravenous) PA Policy to Antibiotics (Injectable) PA Policy.	NA
Annual Revision	No criteria changes.	08/19/2020

NA – Not applicable.

PRIOR AUTHORIZATION POLICY

POLICY: Anticoagulants – Eliquis Prior Authorization Policy

- Eliquis® (apixaban tablets – Bristol-Myers Squibb/Pfizer)

REVIEW DATE: 11/18/2020

OVERVIEW

Eliquis, a Factor Xa inhibitor, is indicated for the following[1]:

- **Non-valvular atrial fibrillation**, to reduce the risk of stroke and systemic embolism.
- **Prophylaxis of deep vein thrombosis (DVT)**, which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.
- **Treatment of DVT and PE**, as well as **reduction in the risk of recurrence of DVT and PE** following initial therapy.

Guidelines

Guidelines are available which support the use of direct oral anticoagulants (DOACs) in their commonly used clinical settings, such as DVT/PE[2-4] and atrial fibrillation[5,6]. In patients who are eligible for a DOAC, these are generally preferred over vitamin K antagonists (e.g., warfarin). It is noted that in the randomized trials in atrial fibrillation, DOACs were consistently at least non-inferior to warfarin regarding the composite of stroke or systemic embolism and were associated with lower risk of serious bleeding.[6]

Anticoagulants and Coronavirus Disease 19 (COVID-19)

Several clinical practice guidelines have been published with regard to use of anticoagulant therapy in the management of COVID-19. In a guideline from the American College of Chest Physicians (CHEST) [June 2, 2020], anticoagulant thromboprophylaxis is suggested over no prophylaxis for acutely ill hospitalized patients with COVID-19.[7] Extended thromboprophylaxis after hospital discharge is not routinely recommended but may be considered for a patient with low bleeding risk, if emerging data on the post-discharge risk of venous thromboembolism (VTE) and bleeding indicate a net benefit of such prophylaxis. Randomized, controlled trials have not been conducted to evaluate the efficacy of various anticoagulants or placebo in COVID-19 patients; however, the guideline notes that most patients with COVID-19 would have been eligible to participate in landmark trials of anticoagulant thromboprophylaxis in acutely ill medical inpatients. According to guidance from the International Society of Thrombosis and Hemostasis (May 27, 2020), extended post-discharge thromboprophylaxis should be considered for all hospitalized patients with COVID-19 who meet high VTE risk criteria.[8] Xarelto® (rivaroxaban tablets) and Bevyxxa® (betrixaban capsules) are cited as treatment options for extended-duration thromboprophylaxis. Likewise, guidance from the Anticoagulation Forum (May 21, 2020) states that for a COVID-19 patient in whom post-discharge prophylaxis is deemed reasonable, an adequately studied and/or approved agent such as Bevyxxa or Xarelto is recommended.

Other Uses with Supportive Evidence

Although data are not robust regarding use of DOACs in off-label thromboembolic-related conditions, CHEST guidelines (2012) suggest anticoagulation for certain patients with superficial vein thrombosis, symptomatic splanchnic thromboses (portal, mesenteric, and/or splenic vein), or symptomatic hepatic vein thrombosis.[2] The guidelines acknowledge the limited available data in these settings, and all are given Grade 2C recommendations (weak recommendation, low-quality evidence). The 2016 CHEST guideline update did not address these conditions or comment on the role of DOACs.[3] The choice of anticoagulant is often individualized based on patient-specific factors; therefore, for certain patients, DOAC use may be considered in practice. Evidence for DOACs is limited for off-label scenarios; in general, agents such as vitamin K antagonists (e.g., warfarin) and low molecular weight heparin have more clinical experience in these settings.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Eliquis. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Eliquis is recommended in those who meet the following criteria:

FDA-Approved Indications

2. **Atrial Fibrillation (or Atrial Flutter).** Approve for 1 year.

3. **Deep Vein Thrombosis in Patients Undergoing Hip or Knee Replacement Surgery, Prophylaxis.** Approve for 60 days.

4. **Deep Vein Thrombosis or Pulmonary Embolism, Treatment.** Approve for 1 year.

5. **Deep Vein Thrombosis or Pulmonary Embolism to Reduce the Risk of Recurrence.** Approve for 1 year.

Other Uses with Supportive Evidence

6. **Treatment or Prevention of Other Thromboembolic-Related Conditions (e.g., superficial vein thrombosis, splanchnic vein thrombosis, hepatic vein thrombosis, prophylaxis of venous thromboembolism in a high-risk patient).** Approve for 6 months if the patient meets one of the following criteria (A or B):
   - **A)** Patient meets one of the following for the condition (i or ii):
     - **i.** Patient has tried warfarin, fondaparinux injection, or a low molecular weight heparin product (e.g., enoxaparin injection, Fragmin® [dalteparin injection]); OR
     - **ii.** Patient has tried Xarelto® (rivaroxaban tablets), Pradaxa® (dabigatran capsules), or Savaysa® (edoxaban tablets); OR
   - **B)** Patient has been started on Eliquis for the treatment of an acute thromboembolic condition.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Eliquis is not recommended in the following situations:

1. **Venous Thromboembolism in an Acutely Ill Medical Patient, Prophylaxis.** (Note: This includes post-discharge thromboprophylaxis for a patient hospitalized with coronavirus disease 19 [COVID-19]). Eliquis has been compared with enoxaparin for post-discharge prophylaxis in acutely ill medical patients; however, superiority vs. enoxaparin was not achieved, and bleeding was increased with Eliquis.[10] Xarelto and Bevyxxa are labeled for prophylaxis of venous thromboembolism in acutely ill medical patients and are supported in clinical practice guidelines, including guidelines which address prophylaxis of venous thromboembolism in COVID-19 patients.[7-9]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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65. Guyatt GH, Akl EA, Crowther M, et al, for the American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:7S-47S.
66. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST Guideline and Expert Panel Report. *Chest*. 2016;149(2):315-352.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Treatment or Prevention of Other Thromboembolic-Related Conditions:** Examples updated to reflect current clinical practice guidelines and provide consistency across anticoagulant prior authorization policies.	11/28/2018
Annual Revision	No criteria changes.	11/13/2019
Annual Revision	**Use After an Acute Coronary Syndrome to Reduce the Potential for Thrombotic Events:** This condition was removed from Conditions Not Recommended for Approval. **Venous Thromboembolism in an Acutely Ill Medical Patient, Prophylaxis:** This was added to Conditions Not Recommended for Approval. Of note, this includes post-discharge thromboprophylaxis in a patient hospitalized with coronavirus disease 19 (COVID-19).	11/18/2020

PRIOR AUTHORIZATION WITH STEP THERAPY POLICY

POLICY: Anticoagulants – Pradaxa Prior Authorization with Step Therapy Policy
- Pradaxa® (dabigatran capsules – Boehringer Ingelheim)

REVIEW DATE: 11/18/2020

OVERVIEW

Pradaxa, a direct thrombin inhibitor, is indicated for the following conditions[1]:
- **Non-valvular atrial fibrillation**, to reduce the risk of stroke and systemic embolism.
- **Prophylaxis of DVT and PE**, in patients who have undergone hip replacement surgery.
- **Treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE)** in patients who have been treated with a parenteral anticoagulant for 5 to 10 days, as well as r**eduction in the risk of recurrence of DVT and PE** in patients who have been previously treated.

Guidelines

Guidelines are available which support the use of direct oral anticoagulants (DOACs) in their commonly used clinical settings, such as DVT/PE[2-4] and atrial fibrillation[5,6]. In patients who are eligible for a DOAC, these are generally preferred over vitamin K antagonists (e.g., warfarin). It is noted that in the randomized trials in atrial fibrillation, DOACs were consistently at least non-inferior to warfarin regarding the composite of stroke or systemic embolism and were associated with lower risk of serious bleeding.[6]

Anticoagulants and Coronavirus Disease 19 (COVID-19)

Several clinical practice guidelines have been published with regard to use of anticoagulant therapy in the management of COVID-19. In a guideline from the American College of Chest Physicians (CHEST) [June 2, 2020], anticoagulant thromboprophylaxis is suggested over no prophylaxis for acutely ill hospitalized patients with COVID-19.[7] Extended thromboprophylaxis after hospital discharge is not routinely recommended but may be considered for a patient with low bleeding risk, if emerging data on the post-discharge risk of venous thromboembolism (VTE) and bleeding indicate a net benefit of such prophylaxis. Randomized, controlled trials have not been conducted to evaluate the efficacy of various anticoagulants or placebo in COVID-19 patients; however, the guideline notes that most patients with COVID-19 would

have been eligible to participate in landmark trials of anticoagulant thromboprophylaxis in acutely ill medical inpatients. According to guidance from the International Society of Thrombosis and Hemostasis (May 27, 2020), extended post-discharge thromboprophylaxis should be considered for all hospitalized patients with COVID-19 who meet high VTE risk criteria.[8] Xarelto® (rivaroxaban tablets) and Bevyxxa® (betrixaban capsules) are cited as treatment options for extended-duration thromboprophylaxis. Likewise, guidance from the Anticoagulation Forum (May 21, 2020) states that for a COVID-19 patient in whom post-discharge prophylaxis is deemed reasonable, an adequately studied and/or approved agent such as Bevyxxa or Xarelto is recommended.

Other Uses with Supportive Evidence

Pradaxa has data supporting its use in prophylaxis after knee replacement surgery.[10-12] Although data are not robust regarding use of DOACs in other off-label thromboembolic-related conditions, CHEST guidelines (2012) suggest anticoagulation for certain patients with superficial vein thrombosis, symptomatic splanchnic thromboses (portal, mesenteric, and/or splenic vein), or symptomatic hepatic vein thrombosis.[2] The guidelines acknowledge the limited available data in these settings, and all are given Grade 2C recommendations (weak recommendation, low-quality evidence). The 2016 CHEST guideline update did not address these conditions or comment on the role of DOACs.[3] The choice of anticoagulant is often individualized based on patient-specific factors; therefore, for certain patients, DOAC use may be considered in practice. Evidence for DOACs is limited for off-label scenarios; in general, agents such as vitamin K antagonists (e.g., warfarin) and low molecular weight heparin have more clinical experience in these settings.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Pradaxa. This policy also contains a Step Therapy component, which has been developed to encourage the use of one Step 1 Product (Eliquis® [apixaban tablets] or Xarelto) prior to Pradaxa (Step 2). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. If the patient meets the criteria for the diagnosis stated but has not tried a Step 1 Product, approvals are provided for both of the Step 1 Products.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Pradaxa is recommended in those who meet the following criteria:

FDA-Approved Indications

7. **Atrial Fibrillation (or Atrial Flutter).** Approve for 1 year if the patient has tried Eliquis or Xarelto.

8. **Deep Vein Thrombosis or Pulmonary Embolism, Treatment.** Approve for 1 year if the patient meets one of the following (A or B):
   A) Patient has tried Eliquis or Xarelto; OR
   B) Patient is currently receiving Pradaxa for this condition.

9. **Deep Vein Thrombosis or Pulmonary Embolism, To Reduce the Risk of Recurrence.** Approve for 1 year if the patient has tried Eliquis or Xarelto.

10. **Deep Vein Thrombosis or Pulmonary Embolism, Prophylaxis Following Hip Replacement Surgery.** Approve for 60 days if the patient meets one of the following (A or B):

A) Patient has tried Eliquis or Xarelto; OR
B) Patient is currently receiving Pradaxa for this condition.

Other Uses with Supportive Evidence

11. Deep Vein Thrombosis in Patients Undergoing Knee Replacement Surgery, Prophylaxis. Approve for 60 days if the patient meets one of the following (A or B):
A) Patient has tried Eliquis or Xarelto; OR
B) Patient is currently receiving Pradaxa for this condition.

12. Treatment or Prevention of Other Thromboembolic-Related Conditions (e.g., superficial vein thrombosis, splanchnic vein thrombosis, hepatic vein thrombosis, prophylaxis of venous thromboembolism in high-risk patients). Approve for 6 months if the patient meets ONE of the following criteria (A or B):
C) Patient meets one of the following for the condition (i or ii):
i. Patient has tried warfarin, fondaparinux, or a low molecular weight heparin (LMWH) product (e.g., enoxaparin, Fragmin® [dalteparin injection]); OR
ii. Patient has tried Eliquis or Xarelto; OR
D) Patient has been started on Pradaxa for the treatment of an acute thromboembolic condition.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Pradaxa is not recommended in the following situations:

3. Venous Thromboembolism in an Acutely Ill Medical Patient, Prophylaxis. (Note: This includes post-discharge thromboprophylaxis for a patient hospitalized with coronavirus disease 19 [COVID-19]). Xarelto and Bevyxxa are labeled for prophylaxis of venous thromboembolism in acutely ill medical patients and are supported in clinical practice guidelines, including guidelines which address prophylaxis of venous thromboembolism in COVID-19 patients.[7-9]

24. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Deep Vein Thrombosis (DVT) in Patients Undergoing Knee Replacement Surgery, Prophylaxis:** Added to Other Uses with Supportive Evidence; previously this was grouped under Treatment or Prevention of Other Thromboembolic-Related Conditions (Other Uses with Supportive Evidence, #6). Criteria were updated to allow completion of therapy for patients started on Pradaxa for this indication. **Treatment or Prevention of Other Thromboembolic-Related Conditions:** Examples updated to reflect current clinical practice guidelines and provide consistency across anticoagulant prior authorization policies.	11/28/2018
Annual Revision	No criteria changes.	11/13/2019
Annual Revision	**Mechanical Prosthetic Heart Valves (To Prevent Thromboembolic Complications):** Removed from Conditions Not Recommended for Approval. **Use after Acute Coronary Syndrome to Reduce the Potential for Thrombotic Events:** Removed from Conditions Not Recommended for Approval. **Venous Thromboembolism in an Acutely Ill Medical Patient, Prophylaxis:** This was added to Conditions Not Recommended for Approval. Of note, this includes post-discharge thromboprophylaxis in a patient hospitalized with coronavirus disease 19 (COVID-19).	11/18/2020
DEU Update	**01/26/2021:** No changes to criteria. The policy was renamed to "Anticoagulants – Pradaxa Prior Authorization with Step Therapy Policy".	NA

PRIOR AUTHORIZATION WITH STEP THERAPY POLICY

POLICY: Anticoagulants – Savaysa Prior Authorization with Step Therapy Policy
- Savaysa® (edoxaban tablets – Daiichi Sankyo)

REVIEW DATE: 11/18/2020

OVERVIEW

Savaysa, a Factor Xa inhibitor, is indicated for the following[1]:
- **Non-valvular atrial fibrillation**, to reduce the risk of stroke and systemic embolism.
- **Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)**, following 5 to 10 days of initial therapy with a parenteral anticoagulant.

Savaysa has a unique Boxed Warning regarding reduced efficacy in non-valvular atrial fibrillation in patients with a creatinine clearance > 95 mL/min; Savaysa should be avoided in these individuals.

Guidelines

Guidelines are available which support the use of direct oral anticoagulants (DOACs) in their commonly used clinical settings, such as DVT/PE[2-4] and atrial fibrillation[5,6]. In patients who are eligible for a DOAC, these are generally preferred over vitamin K antagonists (e.g., warfarin). It is noted that in the randomized trials in atrial fibrillation, DOACs were consistently at least non-inferior to warfarin regarding the composite of stroke or systemic embolism and were associated with lower risk of serious bleeding.[6] In the setting of cancer-associated venous thromboembolism (VTE), both Savaysa and Eliquis® (apixaban tablets) are supported as category 1 recommendations by the National Comprehensive Cancer Network guidelines (version 1.2020 – April 16, 2020).

Anticoagulants and Coronavirus Disease 19 (COVID-19)

Several clinical practice guidelines have been published with regard to use of anticoagulant therapy in the management of COVID-19. In a guideline from the American College of Chest Physicians (CHEST) [June 2, 2020], anticoagulant thromboprophylaxis is suggested over no prophylaxis for acutely ill hospitalized patients with COVID-19.[7] Extended thromboprophylaxis after hospital discharge is not routinely recommended but may be considered for a patient with low bleeding risk, if emerging data on the post-discharge risk of VTE and bleeding indicate a net benefit of such prophylaxis. Randomized, controlled trials have not been conducted to evaluate the efficacy of various anticoagulants or placebo in COVID-19 patients; however, the guideline notes that most patients with COVID-19 would have been eligible to participate in landmark trials of anticoagulant thromboprophylaxis in acutely ill medical inpatients. According to guidance from the International Society of Thrombosis and Hemostasis (May 27, 2020), extended post-discharge thromboprophylaxis should be considered for all hospitalized patients with COVID-19 who meet high VTE risk criteria.[8] Xarelto® (rivaroxaban tablets) and Bevyxxa® (betrixaban capsules) are cited as treatment options for extended-duration thromboprophylaxis. Likewise, guidance from the Anticoagulation Forum (May 21, 2020) states that for a COVID-19 patient in whom post-discharge prophylaxis is deemed reasonable, an adequately studied and/or approved agent such as Bevyxxa or Xarelto is recommended.[9]

Other Uses with Supportive Evidence

Savaysa has data for prophylaxis of VTE after hip replacement surgery.[10] Although data are not robust regarding use of DOACs in other off-label thromboembolic-related conditions, CHEST guidelines (2012) suggest anticoagulation for certain patients with superficial vein thrombosis, symptomatic splanchnic thromboses (portal, mesenteric, and/or splenic vein), or symptomatic hepatic vein thrombosis.[2] The guidelines acknowledge the limited available data in these settings, and all are given Grade 2C recommendations (weak recommendation, low-quality evidence). The 2016 CHEST guideline update did not address these conditions or comment on the role of DOACs.[3] The choice of anticoagulant is often individualized based on patient-specific factors; therefore, for certain patients, DOAC use may be considered in practice. Evidence for DOACs is limited for off-label scenarios; in general, agents such as vitamin K antagonists (e.g., warfarin) and low molecular weight heparin have more clinical experience in these settings.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Savaysa. This policy also contains a Step Therapy component, which has been developed to encourage the use of one Step 1 Product (Eliquis or Xarelto) prior to Savaysa (Step 2). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. If the patient meets the criteria for the diagnosis stated but has not tried a Step 1 Product, approvals are provided for both of the Step 1 Products.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Savaysa is recommended in those who meet the following criteria:

FDA-Approved Indications

13. **Atrial Fibrillation (or Atrial Flutter).** Approve for 1 year if the patient meets both of the following criteria (A and B):
    - **C)** Patient has an estimated creatinine clearance (CrCl) ≤ 95 mL/min; AND
    - **D)** Patient has tried Eliquis or Xarelto.

14. **Deep Vein Thrombosis or Pulmonary Embolism, Treatment.** Approve for 1 year if the patient meets one of the following criteria (A or B):
    - **A)** Patient has tried Eliquis or Xarelto; OR
    - **B)** Patient is currently receiving Savaysa for this condition.

Other Uses with Supportive Evidence

15. **Deep Vein Thrombosis in Patients Undergoing Hip Replacement Surgery, Prophylaxis.** Approve for 60 days if the patient meets one of the following criteria (A or B):
    - **C)** Patient has tried Eliquis or Xarelto; OR
    - **D)** Patient is currently receiving Savaysa for this condition.

16. **Treatment or Prevention of Other Thromboembolic-Related Conditions (e.g., superficial vein thrombosis, splanchnic vein thrombosis, hepatic vein thrombosis, prophylaxis of venous thromboembolism in high-risk patients).** Approve for 6 months if the patient meets ONE of the following criteria (A or B):
    - **E)** Patient meets one of the following for the condition (i or ii):
        - **i.** Patient has tried warfarin, fondaparinux, or a low molecular weight heparin product (e.g., enoxaparin, Fragmin® [dalteparin injection]); OR
        - **ii.** Patient has tried Eliquis or Xarelto; OR
    - **F)** Patient has been started on Savaysa for the treatment of an acute thromboembolic condition.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Savaysa is not recommended in the following situations:

25. **Venous Thromboembolism in an Acutely Ill Medical Patient, Prophylaxis.** (Note: This includes post-discharge thromboprophylaxis for a patient hospitalized with coronavirus disease 19 [COVID-19]). Xarelto and Bevyxxa are labeled for prophylaxis of venous thromboembolism in acutely ill medical patients and are supported in clinical practice guidelines, including guidelines which address prophylaxis of venous thromboembolism in COVID-19 patients.[7-9]

26. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Deep Vein Thrombosis (DVT) or Pulmonary Embolism (PE), Treatment:** Added criterion to allow Savaysa use without previous trial of Xarelto or Eliquis in patients with DVT/PE associated with cancer, based on preference for Savaysa in this use per NCCN guidelines (2.2018). Combined DVT and PE into one indication for consistency across anticoagulant PA policies. **Deep Vein Thrombosis (DVT) in Patients Undergoing Hip Replacement Surgery, Prophylaxis:** Added to Other Uses with Supportive Evidence; previously this was grouped under Treatment or Prevention of Other Thromboembolic-Related Conditions (Other Uses with Supportive Evidence, #4). Criteria were updated to allow for completion of therapy in patients started on Savaysa for this indication. **Treatment or Prevention of Other Thromboembolic-Related Conditions:** Examples updated to reflect current clinical practice guidelines and provide consistency across anticoagulant PA policies.	11/28/2018
Annual Revision	No criteria changes.	11/13/2019
Annual Revision	**Deep Vein Thrombosis or Pulmonary Embolism, Treatment:** Removed the exception criterion for patients with cancer-associated thromboembolism. This is no longer needed as Eliquis also has a category 1 recommendation for use in this setting. **Use after Acute Coronary Syndrome to Reduce the Potential for Thrombotic Events:** Removed from Conditions Not Recommended for Approval. **Venous Thromboembolism in an Acutely Ill Medical Patient, Prophylaxis:** This was added to Conditions Not Recommended for Approval. Of note, this includes post-discharge thromboprophylaxis in a patient hospitalized with coronavirus disease 19 (COVID-19).	11/18/2020
DEU Update	**01/26/2021:** No changes to criteria. The policy was renamed to "Anticoagulants – Savaysa Prior Authorization with Step Therapy Policy".	NA

PRIOR AUTHORIZATION POLICY

POLICY: Anticoagulants – Xarelto Prior Authorization Policy

- Xarelto® (rivaroxaban tablets – Janssen)

REVIEW DATE: 11/18/2020

OVERVIEW

Xarelto, an oral Factor Xa inhibitor, is indicated for the following[1]:

- **Non-valvular atrial fibrillation**, to reduce the risk of stroke and systemic embolism.
- **Prophylaxis of DVT,** which may lead to PE, in patients undergoing knee or hip replacement surgery.
- **Prophylaxis of venous thromboembolism in acutely ill medical patients** at risk for thromboembolic complications not at high risk of bleeding.
- **Reduction in risk of major adverse cardiovascular (CV) events (CV death, myocardial infarction, and stroke)**, in combination with aspirin, in patients with chronic coronary artery disease or peripheral arterial disease.
- **Treatment of deep vein thrombosis (DVT)** and **pulmonary embolism (PE)**, as well as **reduction in the risk of recurrence of DVT and/or PE** in patients at continued risk for recurrent DVT and/or PE after completion of initial treatment.

Guidelines

Guidelines are available which support the use of direct oral anticoagulants (DOACs) in their commonly used clinical settings, such as DVT/PE[2-4] and atrial fibrillation[5,6]. In patients who are eligible for a DOAC, these are generally preferred over vitamin K antagonists (e.g., warfarin). It is noted that in the randomized trials in atrial fibrillation, DOACs were consistently at least non-inferior to warfarin regarding the composite of stroke or systemic embolism and were associated with lower risk of serious bleeding.[6]

Anticoagulants and Coronavirus Disease 19 (COVID-19)

Several clinical practice guidelines have been published with regard to use of anticoagulant therapy in the management of COVID-19. In a guideline from the American College of Chest Physicians (CHEST) [June 2, 2020], anticoagulant thromboprophylaxis is suggested over no prophylaxis for acutely ill hospitalized patients with COVID-19.[7] Extended thromboprophylaxis after hospital discharge is not routinely recommended but may be considered for a patient with low bleeding risk, if emerging data on the post-discharge risk of venous thromboembolism (VTE) and bleeding indicate a net benefit of such prophylaxis. Randomized, controlled trials have not been conducted to evaluate the efficacy of various anticoagulants or placebo in COVID-19 patients; however, the guideline notes that most patients with COVID-19 would have been eligible to participate in landmark trials of anticoagulant thromboprophylaxis in acutely ill medical inpatients. According to guidance from the International Society of Thrombosis and Hemostasis (May 27, 2020), extended post-discharge thromboprophylaxis should be considered for all hospitalized patients with COVID-19 who meet high VTE risk criteria.[8] Xarelto and Bevyxxa (betrixaban capsules) are cited as treatment options for extended-duration thromboprophylaxis. Likewise, guidance from the Anticoagulation Forum (May 21, 2020) states that for a COVID-19 patient in whom post-discharge prophylaxis is deemed reasonable, an adequately studied and/or approved agent such as Bevyxxa or Xarelto is recommended.

Other Uses with Supportive Evidence

Although data are not robust regarding use of DOACs in off-label thromboembolic-related conditions, CHEST guidelines (2012) suggest anticoagulation for certain patients with superficial vein thrombosis, symptomatic splanchnic thromboses (portal, mesenteric, and/or splenic vein), or symptomatic hepatic vein thrombosis.[2] The guidelines acknowledge the limited available data in these settings, and all are given Grade 2C recommendations (weak recommendation, low-quality evidence). The 2016 CHEST guideline update did not address these conditions or comment on the role of DOACs.[3] The choice of anticoagulant is often individualized based on patient-specific factors; therefore, for certain patients, DOAC use may be considered in practice. Evidence for DOACs is limited for off-label scenarios; in general, agents such as vitamin K antagonists (e.g., warfarin) and low molecular weight heparin have more clinical experience in these settings.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Xarelto. All approvals are provided for the approval duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indications

1. **Atrial Fibrillation (or Atrial Flutter).** Approve for 1 year.

2. **Deep Vein Thrombosis in a Patient Undergoing Knee or Hip Replacement Surgery, Prophylaxis.** Approve for 60 days.

3. **Deep Vein Thrombosis or Pulmonary Embolism, Treatment.** Approve for 1 year.

4. **Deep Vein Thrombosis or Pulmonary Embolism, to Reduce the Risk of Recurrence.** Approve for 1 year.

5. **Reduction in Risk of Major Cardiovascular Events**. Approve for 1 year if the patient meets the following criteria (A and B):
   A) Patient has coronary artery disease or peripheral artery disease; AND
   B) Patient will be taking concomitant aspirin at least 75 mg daily.

6. **Venous Thromboembolism in an Acutely Ill Medical Patient, Prophylaxis.** Approve for 60 days. Note: This includes post-discharge thromboprophylaxis for a patient hospitalized with coronavirus disease 19 (COVID-19).

Other Uses with Supportive Evidence

7. **Treatment or Prevention of Other Thromboembolic-Related Conditions (e.g., superficial vein thrombosis, splanchnic vein thrombosis, hepatic vein thrombosis, prophylaxis of venous thromboembolism in a high-risk patient).** Approve for 6 months if the patient meets ONE of the following criteria (A or B):
   A) Patient meets one of the following for the condition (i or ii):
      i. Patient has tried warfarin, fondaparinux or a low molecular weight heparin product (e.g., enoxaparin, Fragmin® [dalteparin injection]); OR
      ii. Patient has tried Eliquis® (apixaban tablets), Pradaxa® (dabigatran capsules), or Savaysa® (edoxaban tablets); OR
   B) Patient has been started on Xarelto for the treatment of an acute thromboembolic condition.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xarelto is not recommended in the following situations:

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Reduction in Risk of Major Cardiovascular (CV) Events, Patients with Coronary Artery Disease (CAD) or Peripheral Artery Disease (PAD):** Added to FDA-approved indications.	10/31/2018
Selected Revision	**Deep Vein Thrombosis (DVT) or Pulmonary Embolism (PE), Treatment:** Combined DVT and PE into one indication for consistency across anticoagulant PA policies (previously listed separately). **Treatment or Prevention of Other Thromboembolic-Related Conditions:** Examples updated to reflect current clinical practice guidelines and provide consistency across anticoagulant PA policies.	11/28/2018
Selected Revision	**Venous Thromboembolism in Acutely Ill Medical Patients, Prophylaxis:** Added to FDA-approved indications.	10/30/2019
Annual Revision	**Use After an Acute Coronary Syndrome to Reduce the Potential for Thrombotic Events:** Removed from Conditions Not Recommended for Approval. Xarelto is indicated to reduce major adverse cardiovascular events in patients with coronary artery disease or peripheral artery disease. Individuals with acute coronary syndromes meet criteria for coronary artery disease.	11/13/2019
Annual Revision	**Reduction in Risk of Major Cardiovascular Events:** The phrase "coronary artery disease or peripheral artery disease" was moved from condition title into criteria. **Venous Thromboembolism in an Acutely Ill Medical Patient, Prophylaxis:** A note was added to clarify that this includes post-discharge thromboprophylaxis for a patient hospitalized with coronavirus disease 2019 (COVID-19).	11/18/2020

PRIOR AUTHORIZATION POLICY

POLICY: Antiepileptics – Banzel Prior Authorization Policy

- Banzel® (rufinamide tablets and oral suspension – Eisai)

REVIEW DATE: 09/16/2020

OVERVIEW

Banzel is indicated for adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome in pediatric patients ≥ 1 year of age and in adults.[1]

Although Banzel is only FDA-approved for use in Lennox-Gastaut Syndrome, clinical trial data indicate the drug may also be beneficial as adjunctive treatment of refractory focal epilepsy.[2] A review of six clinical trials found that Banzel when used as an add-on treatment was effective in reducing seizure frequency in patients with drug-resistant focal epilepsy.

Banzel is a triazole derivative structurally unrelated to currently marketed antiepileptic drugs (AEDs).[1] The precise mechanism by which rufinamide exerts its antiepileptic effect is not known. *In vitro* studies suggest that the primary mechanism of action of rufinamide is modulation of the activity of sodium channels and, in particular, prolongation of the inactive state of the channel. Banzel is contraindicated for use in patients with Familial Short QT syndrome. Banzel should be used cautiously with other drugs that shorten the QT interval.

Disease Overview

Lennox-Gastaut syndrome (LGS), a severe epileptic and developmental encephalopathy, is associated with a high rate of morbidity and mortality.[3,4] LGS most often begins between 3 years and 5 years of age and

comprises approximately 3% to 4% of childhood epilepsies.[3-6] Affected children experience several different types of seizures, most commonly atonic seizures (sudden loss of muscle tone and limpness, also called drop seizures) and tonic seizures (increased muscle tone and muscle stiffness).[3,6] The three main forms of treatment of LGS are antiepileptic drugs (AEDs), dietary therapy (typically the ketogenic diet), and device/surgery (e.g., vagus nerve stimulation, corpus callosotomy).[6] None of the therapies are effective in all cases of LGS and the disorder has proven particularly resistant to most therapeutic options. The choice of treatment should take into consideration the patient's age and other associated conditions.

Guidelines/Recommendations

Lennox-Gastaut syndrome. Currently, the FDA-approved drugs for this condition are Epidiolex® (cannabidiol oral solution), felbamate, lamotrigine, Banzel, topiramate, and clobazam.[7] Despite the lack of level I or level II evidence, valproic acid remains a mainstay in treatment.[5,6,8] If valproic acid does not provide adequate seizure control, which is almost always the case, lamotrigine should be added as the first adjunctive therapy.[4] If the combination regimen of valproic acid and lamotrigine does not provide adequate control, then Banzel should be initiated and either valproic acid or lamotrigine should be discontinued. If seizure control is still not achieved, the next adjunctive therapies to consider are topiramate, clobazam, and felbamate. There are limited evidence for the use of levetiracetam, zonisamide, and Fycompa® (perampanel tablet, oral suspension). Where possible, no more than two AEDs should be used concomitantly; use of multiple AEDs raise the risk of side effects and/or drug-drug interactions.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Banzel. Because of the specialized skills required for evaluation and diagnosis of patients treated with Banzel as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Banzel to be prescribed by, or in consultation with, a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Banzel is recommended in those who meet the following criteria:

FDA-Approved Indications

4. **Lennox-Gastaut Syndrome.** Approve for the duration noted below if the patient meets ONE of the following criteria (A or B):
   - **A)** Initial Therapy: Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient is ≥ 1 year of age; AND
     - **ii.** Patient has tried and/or is concomitantly receiving at least two other antiepileptic drugs; AND
       Note: Examples of antiepileptic drugs include valproic acid, gabapentin, phenytoin, carbamazepine, oxcarbazepine, lacosamide, levetiracetam, zonisamide, Fycompa (perampanel tablet or oral suspension), vigabatrin, lamotrigine, topiramate, clobazam, Diacomit (stiripentol capsules or oral suspension), Epidiolex (cannabidiol oral solution), and felbamate.
     - **iii.** The medication is prescribed by, or in consultation with, a neurologist.
   - **B)** Patient is Currently Receiving Banzel: Approve for 1 year if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.

Other Uses with Supportive Evidence

2. **Treatment-Refractory Seizures/Epilepsy.** Approve for the duration noted below if the patient meets ONE of the following criteria (A or B):
   - **A)** Initial Therapy: Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient is ≥ 1 years of age; AND
     - **ii.** Patient has tried and/or is concomitantly receiving at least two other antiepileptic drugs; AND
       Note: Examples of antiepileptic drugs include valproic acid, gabapentin, phenytoin, carbamazepine, oxcarbazepine, lacosamide, levetiracetam, zonisamide, Fycompa (perampanel tablet or oral suspension), vigabatrin, lamotrigine, topiramate, clobazam, Diacomit (stiripentol capsules or oral suspension), Epidiolex (cannabidiol oral solution), and felbamate.
     - **iii.** The medication is prescribed by, or in consultation with, a neurologist.
   - **B)** Patient is Currently Receiving Banzel: Approve for 1 year if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Banzel is not recommended in the following situations:

27. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	09/18/2019
Annual Revision	No change to criteria.	09/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Antiepileptics – Clobazam Products Prior Authorization Policy

- Onfi® (clobazam tablets and oral suspension – Lundbeck, generics)
- Sympazan™ (clobazam oral soluble film – Aquestive Therapeutics)

REVIEW DATE: 11/18/2020

OVERVIEW

All forms of clobazam are indicated for the adjunctive treatment of seizures associated with **Lennox-Gastaut syndrome** (LGS) in patients ≥ 2 years of age.[1,2]

Clobazam is a benzodiazepine.[1,2] The exact mechanism of action is not fully understood but is thought to involve potentiation of gamma-aminobutyric acid (GABA)ergic neurotransmission resulting from binding at the benzodiazepine site of the $GABA_A$ receptor.

Disease Overview

Lennox-Gastaut syndrome (LGS), a severe epileptic and developmental encephalopathy, is associated with a high rate of morbidity and mortality.[3,4] LGS most often begins between 3 and 5 years of age and comprises approximately 4% to 10% of childhood epilepsies; the prevalence is 0.26 per 1,000 people.[3-6] Children may develop normally before onset of seizures and then lose previously acquired skills (psychomotor regression), and because the seizures associated with LGS are usually resistant to treatment, intellectual impairment and learning problems may worsen over time.[6] Affected children experience several different types of seizures, most commonly atonic seizures (sudden loss of muscle tone and limpness, also called drop seizures) and tonic seizures (increased muscle tone and muscle stiffness).[3,6] The three main forms of treatment of LGS are antiepileptic drugs (AEDs), dietary therapy (typically the ketogenic diet), and device/surgery (e.g., Vagus nerve stimulation, corpus callosotomy).[6] None of the therapies are effective in all cases of LGS and the disorder has proven particularly resistant to most therapeutic options. The choice of treatment should take into consideration the patient's age and other associated conditions.

Dravet syndrome is a rare genetic epileptic encephalopathy (dysfunction of the brain) marked with frequent and/or prolonged seizures.[7,8] It's been estimated that 1 out of 15,700 infants born in the US are affected with Dravet syndrome. The seizures generally begin in the first year of life in an otherwise healthy infant. Affected individuals can develop many seizure types: myoclonic, tonic-clonic, absence, atypical absence, atonic, focal aware or impaired awareness (previously called partial seizures), and status epilepticus.[8] As the seizures continue, most of the children develop some level of developmental disability and other conditions associated with the syndrome. Two or more AEDs are often needed to control the seizures; most of the seizures are refractory to medications. The goals of treatment are cessation of prolonged convulsions, reductions in overall seizure frequency, and minimization of treatment side effects.[9,10] Some patients respond to the ketogenic diet and/or vagus nerve stimulation.

Guidelines/Recommendations

Lennox-Gastaut Syndrome

Currently, the FDA-approved drugs for this condition are Epidiolex® (cannabidiol oral solution), felbamate, lamotrigine, Banzel® (rufinamide tablet, oral suspension), topiramate, and clobazam.[11] Despite the lack of level I or level II evidence, valproic acid remains a mainstay in treatment.[5,6,12] If valproic acid does not provide adequate seizure control, which is almost always the case, lamotrigine should be added as the first adjunctive therapy.[4] If the combination regimen of valproic acid and lamotrigine does not provide adequate control, then Banzel should be initiated and either valproic acid or lamotrigine should be discontinued. If seizure control is still not achieved, the next adjunctive therapies to consider are topiramate, clobazam, and felbamate. There are limited evidence for the use of levetiracetam, zonisamide, and Fycompa® (perampanel tablet, oral suspension). Where possible, no more than two AEDs should be used concomitantly; use of multiple AEDs raise the risk of side effects and/or drug-drug interactions.

Dravet Syndrome

Valproic acid and clobazam are considered to be the first-line treatment for Dravet syndrome.[7,9,10] If seizure control is suboptimal, Diacomit® (stiripentol capsules), Epidiolex® (cannabidiol oral solution), Fintepla® (fenfluramine oral solution), and topiramate are treatment options. Ketogenic diet is moderately effective

and can also be considered second-line. If control is still inadequate, other therapies to consider are clonazepam, levetiracetam, and zonisamide. Drugs that should be avoided in Dravet syndrome include sodium channel blockers (e.g., carbamazepine, oxcarbazepine, lamotrigine, and phenytoin), Sabril® (vigabatrin tablet, oral packet), and tiagabine.

The American Academy of Neurology (AAN) and the American Epilepsy Society published a guideline update for treatment-resistant epilepsy (2018) stating that clobazam is probably effective as add-on therapy for LGS and is possibly effective as add-on therapy for treatment-resistant adult focal epilepsy.[13] Adjunctive therapy with clobazam has been effective in the treatment of uncontrolled or refractory epilepsy in adults and children.[14] If first-line treatment is ineffective or not tolerated, clobazam has been used as adjunctive treatment of refractory focal seizures (partial seizure and localization-related seizure) in children, young adults, and adults; adjunctive treatment of generalized tonic-clonic seizures in children, young adults, and adults; and adjunctive treatment of children and young adults with benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome or late-onset childhood occipital epilepsy (Gastaut type).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of clobazam. Because of the specialized skills required for evaluation and diagnosis of patients treated with clobazam as well as the monitoring required for adverse events and long-term efficacy, initial approval requires clobazam to be prescribed by, or in consultation with, a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of clobazam is recommended in those who meet the following criteria:

FDA-Approved Indications

5. Lennox-Gastaut Syndrome. Approve for 1 year if the patient meets ONE of the following criteria (A or B):

C) Initial Therapy. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
- **i.** Patient is ≥ 2 years of age; AND
- **ii.** Patient has tried and/or is concomitantly receiving at least two other antiepileptic drugs (e.g., valproic acid, levetiracetam, zonisamide, perampanel, vigabatrin, others) OR one of lamotrigine, topiramate, rufinamide, felbamate, or Epidiolex; AND
- **iii.** Clobazam is prescribed by, or in consultation with, a neurologist.

D) Patient is Currently Receiving Clobazam. Approve for 1 year if the patient is responding to therapy, as determined by the prescriber.
Note: Examples of therapy response include reduced seizure severity, frequency, and/or duration from baseline [prior to initiation of clobazam].

Other Uses with Supportive Evidence

6. Dravet Syndrome. Approve for 1 year if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 1 year if the patient meets the following criteria (i and ii)
- **i.** Patient is ≥ 2 years of age; AND
- **ii.** Clobazam is prescribed by, or in consultation with, a neurologist.

B) Patient is Currently Receiving Clobazam. Approve for 1 year if the patient is responding to therapy, as determined by the prescriber.
Note: Examples of therapy response include reduced seizure severity, frequency, and/or duration from baseline [prior to initiation of clobazam].

3. Treatment-Refractory Seizures/Epilepsy. Approve for 1 year if the patient meets ONE of the following criteria (A or B):

C) Initial Therapy. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
- **i.** Patient is ≥ 2 years of age; AND
- **ii.** Patient has tried and/or is concomitantly receiving at least two other antiepileptic drugs; AND
  Note: Examples are valproic acid, lamotrigine, topiramate, clonazepam, levetiracetam, zonisamide, Banzel, felbamate.
- **iii.** Clobazam is prescribed by, or in consultation with, a neurologist.

D) Patient is Currently Receiving Clobazam. Approve for 1 year if the patient is responding to therapy, as determined by the prescriber.
Note: Examples of therapy response include reduced seizure severity, frequency, and/or duration from baseline [prior to initiation of clobazam].

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of clobazam is not recommended in the following situations:

28. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	11/07/2018
Annual Revision	In each of the three approved conditions (Lennox-Gastaut Syndrome, Dravet Syndrome, and Treatment-Refractory Seizures/Epilepsy), the term "prescribing physician" is being changed to "prescriber".	11/20/2019
Annual Revision	No criteria changes.	11/18/2020

PRIOR AUTHORIZATION POLICY

POLICY: Antiepileptics – Diacomit Prior Authorization Policy

- Diacomit® (stiripentol capsules and powder for oral suspension – Biocodex)

REVIEW DATE: 02/03/2021

OVERVIEW

Diacomit, an antiepileptic drug (AED), is indicated for the treatment of seizures associated with **Dravet syndrome** in patients ≥ 2 years of age taking clobazam.[1] There are no clinical data to support the use of Diacomit as monotherapy in Dravet syndrome.

Disease Overview

Dravet syndrome is a rare genetic epileptic encephalopathy (dysfunction of the brain) marked with frequent and/or prolonged seizures.[2,3] The seizures generally begin in the first year of life in an otherwise healthy infant. Affected individuals can develop many seizure types: myoclonic, tonic-clonic, absence, atypical absence, atonic, focal aware or impaired awareness (previously called partial seizures), and status epilepticus.[3] Two or more AEDs are often needed to control the seizures; most of the seizures are refractory to medications. The goals of treatment are cessation of prolonged convulsions, reductions in overall seizure frequency, and minimization of treatment side effects.[4,5]

Clinical Efficacy in Other Refractory Seizures

In one study (n = 212), Diacomit was studied in children with different types of epilepsy syndromes (including Lennox-Gastaut Syndrome [LGS]; infantile spasms; infection-related or anoxo-ischemic epilepsy syndromes; tuberous sclerosis complex; Sturge-Weber syndrome; Doose syndrome; cortical malformation/dysplasia; and epilepsy with myoclonic absences) whose seizures were refractory to more than two AEDs (including Sabril).[6] In the 88 patients who completed the 3-month placebo-controlled study, 56.8% of patients with partial epilepsy responded (with 14% becoming seizure free) compared with 41.9% of patients with generalized epilepsy and 38.4% of patients with myoclonic epilepsy. Diacomit has also been administered to patients with epileptic encephalopathies associated with SCN1A mutations or other sodium channel mutations under compassionate use protocalls.[7] A single-blind, exploratory trial evaluated Diacomit in combination with standard treatment in 16 patients with LGS and eight patients with symptomatic generalized epilepsy of the Lennox-Gastaut type.[8] There were 15 evaluable patients with LGS. The overall results identified some benefit for LGS where 60% of patients were responders (based on 50% responder rate). Diacomit treatment produced a mean 62% seizure reduction and median -80% reduction from baseline. Additionally, a published study of Diacomit added to carbamazepine in childhood partial epilepsy (n = 67) demonstrated seizure response in 32 patients with conditions including herpetic encephalitis, LGS, and tuberous sclerosis complex.[9]

Guidelines/Recommendations

At this time, there are three drugs approved for the treatment of seizures associated with Dravet syndrome: Diacomit, Epidiolex® (cannabidiol oral solution), and Fintepla® (fenfluramine oral solution).[1,10,11] An expert panel considers valproic acid and clobazam are considered to be the first-line treatment for Dravet syndrome.[5] If seizure control is suboptimal, Diacomit and topiramate are second-line treatment. Ketogenic diet is moderately effective and can also be considered second-line. The Dravet Foundation states that Diacomit, Epidiolex, and Fintepla are considered first-line agents for the treatment of Dravet syndrome.[2] If control is still inadequate, other therapies to consider are clonazepam, levetiracetam, and zonisamide.[2,4,5] Sodium channel blockers (e.g., carbamazepine, oxcarbazepine, lamotrigine, and phenytoin) can worsen seizures in Dravet syndrome. Additionally, vigabatrin and tiagabine may increase the frequency of myoclonic seizures and should be avoided.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Diacomit. Because of the specialized skills required for evaluation and diagnosis of patients treated with Diacomit as well as the monitoring required for adverse events and efficacy, initial approval requires Diacomit to be prescribed by, or in consultation with, a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Diacomit is recommended in those who meet the following criteria:

FDA-Approved Indications

7. Dravet Syndrome. Approve for 1 year if the patient meets ONE of the following criteria (A or B):

C) Initial Therapy: Approve for 1 year if the patient meets the following criteria (i, ii, and iii):

- **i.** Patient is ≥ 2 years of age; AND
- **ii.** Patient meets ONE of the following criteria (a or b):
  - **a)** Patient is taking concomitant clobazam; OR
  - **b)** Patient is unable to take clobazam due to adverse events as determined by the prescriber; AND
- **iii.** The medication is prescribed by, or in consultation with, a neurologist; OR

D) Patient is Currently Receiving Diacomit: Approve for 1 year if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.

Other Uses with Supportive Evidence

4. Treatment-Refractory Seizures/Epilepsy [specific rare conditions] (i.e., Lennox-Gastaut Syndrome; infantile spasms; tuberous sclerosis complex; Sturge-Weber syndrome; Doose syndrome; infection-related or anoxo-ischemic epilepsy syndromes; cortical malformation/dysplasia; epileptic encephalopathies associated with sodium channel mutations; and epilepsy with myoclonic absences). Approve for 1 year if the patient meets ONE of the following criteria (A or B):

E) Initial Therapy: Approve for 1 year if the patient meets the following criteria (i, ii, and iii)

- **iv.** Patient is ≥ 2 years of age; AND
- **v.** Patient has tried at least two other antiepileptic drugs; AND

Note: Examples of other antiepileptic drugs include valproic acid, lamotrigine, topiramate, clonazepam, Banzel® (rufinamide tablet, oral suspension), felbamate, clobazam, Fycompa® (perampanel tablet, oral suspension), vigabatrin, levetiracetam, zonisamide, others.

vi. The medication is prescribed by, or in consultation with, a neurologist; OR

F) Patient is Currently Receiving Diacomit: Approve for 1 year if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Diacomit is not recommended in the following situations:

29. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/03/2019
Annual Revision	Prescribing physician was changed to prescriber throughout the criteria as needed. **Treatment-Refractory Seizures/Epilepsy, Including Lennox-Gastaut Syndrome**: Examples of other antiepileptic drugs were removed from the criteria and changed to a note.	01/29/2020
Selected Revision	**Treatment-Refractory Seizures/Epilepsy**: This is now limited to specific rare conditions. The specific rare conditions are Lennox-Gastaut Syndrome; infantile spasms; tuberous sclerosis complex; Sturge-Weber syndrome; Doose syndrome; infection-related or anoxo-ischemic epilepsy syndromes; cortical malformation/dysplasia; epileptic encephalopathies associated with sodium channel mutations; and epilepsy with myoclonic absences.	05/20/2020
Annual Revision	No criteria changes.	02/03/2021

PRIOR AUTHORIZATION POLICY

POLICY: Antiepileptics – Epidiolex Prior Authorization Policy

- Epidiolex® (cannabidiol oral solution – GW Pharmaceuticals)

REVIEW DATE: 02/03/2021

OVERVIEW

Epidiolex is indicated for the treatment of seizures in patients ≥ 1 years of age associated with:[1]

- **Dravet syndrome**.

- **Lennox-Gastaut syndrome**.
- **Tuberous sclerosis complex**.

Disease Overview

Dravet syndrome is a rare genetic epileptic encephalopathy marked with frequent and/or prolonged seizures.[2,3] The seizures generally begin in the first year of life in an otherwise healthy infant. Affected individuals can develop many seizure types: myoclonic, tonic-clonic, absence, atypical absence, atonic, focal aware or impaired awareness (previously called partial seizures), and status epilepticus.[3] Two or more antiepileptic drugs (AEDs) are often needed to control the seizures; most of the seizures are refractory to medications. The goals of treatment are cessation of prolonged convulsions, reductions in overall seizure frequency, and minimization of treatment side effects.[4,5]

Lennox-Gastaut syndrome, a severe epileptic and developmental encephalopathy, is associated with a high rate of morbidity and mortality.[6,7] Lennox-Gastaut syndrome most often begins between 3 and 5 years of age.[6-9] Affected children experience several different types of seizures, most commonly atonic seizures (sudden loss of muscle tone and limpness) and tonic seizures.[6,9] The three main forms of treatment of Lennox-Gastaut syndrome are AEDs, dietary therapy (typically the ketogenic diet), and device/surgery (e.g., vagus nerve stimulation, corpus callostomy).[9] None of the therapies are effective in all cases of Lennox-Gastaut syndrome and the disorder has proven particularly resistant to most therapeutic options.

Tuberous sclerosis complex is a rare, genetic disease that causes non-cancerous (benign) tumors to grow in the brain and on other vital organs such as the kidneys, heart, eyes, lungs, and skin.[10] It can result in a combination of symptoms including seizures, impaired intellectual development, autism, behavioral problems, skin abnormalities, and kidney disease. Seizures affect most individuals with tuberous sclerosis complex at some point during their life and can be difficult to control.

Clinical Efficacy in Other Refractory Seizures

In 2014, an expanded access program was initiated to provide Epidiolex to patients with treatment-resistant epilepsy. Of the 607 patients included in a published review, 174 patients were diagnosed with Dravet syndrome or Lennox-Gastaut syndrome, and 433 patients were diagnosed with other conditions, including CDKL5 deficiency disorder, Dup15q, Aicardi, and Doose syndromes; febrile infection-related epilepsy syndromes; tuberous sclerosis complex; Sturge-Weber syndrome; lissencephaly; cortical malformation/dysplasia; and myoclonic absence.[14] The patients enrolled in the study had severe, intractable, childhood-onset treatment-resistant epilepsy and were on stable doses of AEDs for 4 weeks before starting Epidiolex as add-on therapy. The initial dose of Epidiolex was 2 to 10 mg/kg/day (taken as two divided doses) and gradually titrated until intolerance or to a maximum dose of 25 mg/kg/day or 50 mg/kg/day, depending upon treatment site. After 12 weeks of treatment, Epidiolex was associated with 51% and 48% reductions in median monthly convulsive and total seizures, respectively. In a cohort of 132 patients (72 children, 60 adults) with treatment-resistant epilepsy, bi-weekly seizure frequency decreased from a mean of 144.4 at entry to 52.2 at 12 weeks ($P = 0.01$) and remained stable thereafter.[15] Of note, patients with a diagnosis of Lennox-Gastaut syndrome or Dravet syndrome were initially excluded because of preferential enrollment into the randomized clinical trials; once these trials were closed for enrollment, patients with these syndromes were also enrolled. In a separate cohort of patients with CDKL5 deficiency disorder and Aicardi, Doose, and Dup15q syndromes ($n = 46$), the percent change in median convulsive seizure frequency decreased from baseline to Week 12 by 51.4% and by 59.1% at Week 48.[16] There was a significant difference between the percent changes in monthly convulsive seizure

frequency during baseline and Week 12 (P = 0.00001), with no difference in seizure percent change between Weeks 12 and 48. Of the 55 patients in the safety group, 27% of patients withdrew by Week 144 due to adverse effects (n = 4), lack of efficacy (n = 9), withdrawn consent (n = 1), and lost to follow-up (n = 1).

Guidelines/Recommendations

Dravet Syndrome

At this time, there are three drugs approved for the treatment of seizures associated with Dravet syndrome: Epidiolex, Diacomit® (stiripentol capsules, powder for oral suspension), and Fintepla® (fenfluramine) oral solution).[1,11,17] An expert panel considers valproic acid and clobazam to be the first-line treatment for Dravet syndrome.[4] If seizure control is suboptimal, Diacomit and topiramate are second-line treatment. Ketogenic diet is moderately effective and can also be considered second-line. The Dravet Foundation states that Diacomit, Epidiolex, and Fintepla are considered first-line agents for the treatment of Dravet syndrome.[2] If control is still inadequate, other therapies to consider are clonazepam, levetiracetam, and zonisamide.[2,4] Sodium channel blockers (e.g., carbamazepine, oxcarbazepine, lamotrigine, and phenytoin can worsen seizures in Dravet syndrome. Additionally, vigabatrin and tiagabine may increase the frequency of myoclonic seizures and should be avoided.

Lennox-Gastaut Syndrome

Currently, the FDA-approved drugs for this condition are felbamate, Banzel® (rufinamide tablet, oral suspension), topiramate, and clobazam.[12] Despite the lack of level I or level II evidence, valproic acid remains a mainstay in treatment.[8,9,13] If valproic acid does not provide adequate seizure control, which is almost always the case, lamotrigine should be added as the first adjunctive therapy.[7] If the combination regimen of valproic acid and lamotrigine does not provide adequate control, then Banzel should be initiated and either valproic acid or lamotrigine should be discontinued. If seizure control is still not achieved, the next adjunctive therapies to consider are topiramate, clobazam, and felbamate. There is limited evidence for the use of levetiracetam, zonisamide, and Fycompa® (perampanel tablet, oral suspension). Where possible, no more than two AEDs should be used concomitantly; use of multiple AEDs raise the risk of side effects and/or drug-drug interactions.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Epidiolex. Because of the specialized skills required for evaluation and diagnosis of patients treated with Epidiolex as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Epidiolex to be prescribed by, or in consultation with, a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Epidiolex is recommended in those who meet the following criteria:

FDA-Approved Indications

8. Dravet Syndrome. Approve if the patient meets ONE of the following criteria (A or B):
E) Initial Therapy: Approve for 1 year if the patient meets the following criteria (i, ii, and iii)
iv. Patient is ≥ 1 years of age; AND
v. Patient meets ONE of the following criteria (a or b):
i. Patient has tried at least two other antiepileptic drugs; OR
Note: Examples of other antiepileptic drugs include valproic acid, topiramate, clonazepam, levetiracetam, zonisamide.
ii. Patient has tried one of Diacomit or clobazam; AND
vi. The medication is prescribed by, or in consultation with, a neurologist.
F) Patient is Currently Receiving Epidiolex: Approve for 1 year if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.

9. Lennox-Gastaut Syndrome. Approve if the patient meets ONE of the following criteria (A or B):
E) Initial Therapy: Approve for 1 year if the patient meets the following criteria (i, ii, and iii)
i. Patient is ≥ 1 years of age; AND
ii. Patient meets ONE of the following criteria (a or b):
a) Patient has tried at least two other antiepileptic drugs; OR
Note: Examples of other antiepileptic drugs include valproic acid, levetiracetam, zonisamide, Fycompa, vigabatrin.
b) Patient has tried one of lamotrigine, topiramate, Banzel, felbamate, clobazam; AND
iii. The medication is prescribed by, or in consultation with, a neurologist.
F) Patient is Currently Receiving Epidiolex: Approve for 1 year if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.

10. Tuberous Sclerosis Complex. Approve if the patient meets ONE of the following criteria (A or B):
A) Initial Therapy: Approve for 1 year if the patient meets the following criteria (i, ii, and iii)
i. Patient is ≥ 1 years of age; AND
ii. Patient has tried at least two other antiepileptic drugs; AND
Note: Examples of other antiepileptic drugs include valproic acid, lamotrigine, topiramate, clonazepam, levetiracetam, zonisamide, Banzel, felbamate, clobazam, Fycompa, vigabatrin, everolimus.
iii. The medication is prescribed by, or in consultation with, a neurologist.
B) Patient is Currently Receiving Epidiolex: Approve for 1 year if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.

Other Uses with Supportive Evidence

5. Treatment-Refractory Seizures/Epilepsy [specific rare conditions] (i.e., CDKL5 deficiency disorder; Dup15q, Aicardi, or Doose syndromes; febrile infection-related epilepsy syndromes; Sturge-Weber syndrome; lissencephaly; cortical malformation/dysplasia; and epilepsy with myoclonic absences). Approve if the patient meets ONE of the following criteria (A or B):
G) Initial Therapy: Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
vii. Patient is ≥ 1 years of age; AND

viii. Patient has tried at least two other antiepileptic drugs; AND

Note: Examples of other antiepileptic drugs include valproic acid, lamotrigine, topiramate, clonazepam, levetiracetam, zonisamide, Banzel, felbamate, clobazam, Fycompa, vigabatrin, others.

ix. The medication is prescribed by, or in consultation with, a neurologist.

H) Patient is Currently Receiving Epidiolex: Approve for 1 year if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Epidiolex is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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121. Fintepla® oral solution [prescribing information]. Emeryville CA: Zogenix Inc; June 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	Revised Dravet syndrome criterion regarding previous drug use such that use of clobazam can lead to an approval: Epidiolex can be approved if patient has tried at least two other AEDs (e.g., valproic acid, topiramate, clonazepam, levetiracetam, zonisamide, others) OR one of Diacomit or clobazam	01/03/2019

Annual Revision	"Prescribing physician" was changed to "prescriber" throughout the criteria as needed. Also, examples of other antiepileptic drugs were removed from the criteria and changed to notes in all three of the approved conditions.	01/29/2020
Update	4/9/2020: Epidiolex is no longer a controlled substance, so reference to it being a Schedule V controlled substance was removed.	--
Selected Revision	For the approval condition of Treatment-Refractory Seizures/Epilepsy, this is now limited to specific rare conditions. The specific rare conditions are tuberous sclerosis complex; CDKL5 deficiency disorder; Dup15q, Aicardi, or Doose syndromes; febrile infection-related epilepsy syndromes; Sturge-Weber syndrome; lissencephaly; cortical malformation/dysplasia; and epilepsy with myoclonic absences.	05/20/2020
Selected Revision	Criteria for a new FDA-approved indication was added for tuberous sclerosis complex and this condition was removed from the approval condition of Treatment-Refractory Seizures/Epilepsy [specific rare conditions] under Other Uses with Supportive Evidence. For the approval conditions of Lennox-Gastaut syndrome, Dravet syndrome, and Treatment-Refractory Seizures/Epilepsy [specific rare conditions], criteria was revised to approve for children ≥ 1 year of age from ≥ 2 years of age based on expanded age indications.	08/12/2020
Annual Revision	No criteria changes.	02/03/2021

PRIOR AUTHORIZATION POLICY

POLICY: Antiepileptics – Fintepla Prior Authorization Policy

- Fintepla® (fenfluramine oral solution – Zogenix)

REVIEW DATE: 07/15/2020

OVERVIEW

Fintepla, a serotonin 5-hydroxytryptamine subtype 2 (5-HT_2) agonist, is indicated for the treatment of seizures associated with Dravet syndrome in patients ≥ 2 years of age.[1]

Disease Overview

Dravet syndrome is a rare genetic epileptic encephalopathy (dysfunction of the brain) marked with frequent and/or prolonged seizures.[2,3] It is estimated that 1 out of 15,700 infants born in the US are affected with Dravet syndrome. The seizures generally begin in the first year of life in an otherwise healthy infant. Affected individuals can develop many seizure types: myoclonic, tonic-clonic, absence, atypical absence, atonic, focal aware or impaired awareness (previously called partial seizures), and status epilepticus.[3] As the seizures continue, most of the children develop some level of developmental disability and other conditions associated with the syndrome. Two or more antiepileptic drugs (AEDs) are often needed to control the seizures; most of the seizures are refractory to medications. The goals of treatment are cessation of prolonged convulsions, reductions in overall seizure frequency, and minimization of treatment side effects.[4,5] Some patients respond to the ketogenic diet and/or vagus nerve stimulation.

Guidelines

Fintepla is not mentioned in the treatment recommendations. Clobazam and valproate (all forms) are the optimal first-line medications and treatment should be initiated with one of these agents and the other added if control remains suboptimal.[6] Diacomit® (stiripentol capsule and powder for oral suspension) and topiramate are optimal second-line medications and should be used if seizure control remains poor after use of both first-line therapies. Ketogenic diet is moderately effective and can be considered second-line. Clonazepam, levetiracetam, and zonisamide are moderately effective if patients fail to respond to the first- and second-line therapies. Medical marijuana is moderately effective for Dravet syndrome (although there is no consensus regarding the specific type/concentration of medical marijuana); and all patients need a home rescue medication and seizure protocol. Carbamazepine, oxcarbazepine, lamotrigine, phenytoin, Sabril® (vigabatrin tablet and oral packet), and tiagabine should be avoided in these patients as these medications can exacerbate seizures in Dravet syndrome.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Fintepla. Because of the specialized skills required for evaluation and diagnosis of patients treated with Fintepla as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Fintepla to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Fintepla is recommended in those who meet the following criteria:

FDA-Approved Indications

16. Dravet Syndrome. Approve if the patient meets ONE the following criteria (A or B):

- **A)** Initial Therapy: Approve for 1 year if the patient meets the following (i, ii, and iii):
  - **i.** Patient is ≥ 2 years of age; AND
  - **ii.** Patient meets ONE of the following (a or b):
    - **a)** Patient has tried or is concomitantly receiving at least two other antiepileptic drugs; OR
      Note: Examples of other antiepileptic drugs include valproic acid, clobazam, topiramate, clonazepam, levetiracetam, zonisamide.
    - **b)** Patient has tried or is concomitantly receiving one of Epidiolex or Diacomit; AND
  - **iii.** Fintepla is prescribed by or consultation with a neurologist; OR
- **B)** Patient is Currently Receiving Fintepla: Approve for 1 year if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Fintepla is not recommended in the following situations:

11. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

62. Fintepla® oral solution [prescribing information]. Emeryville, CA: Zogenix, Inc.; June 2020.
63. Dravet Foundation – Dravet Syndrome. Available at: https://www.dravetfoundation.org/what-is-dravet-syndrome/. Accessed on June 29, 2020.
64. Shafer PO. Epilepsy Foundation – Dravet Syndrome. Updated September 2, 2018. Available at: http://www.epilepsy.com/learn/types-epilepsy-syndromes/dravet-syndrome. Accessed on June 29, 2020.
65. Wirrell EC, Laux L, Donner, et al. Optimizing the diagnosis and management of Dravet syndrome: recommendations from a North American Consensus Panel. *Pediatr Neurol*. 2017;68:18-34.
66. Knupp KG1, Wirrell EC. Treatment Strategies for Dravet Syndrome. *CNS Drugs*. 2018;32(4):335-350.
67. Wirrell EC, Laux L, Donner E, et al. Optimizing the diagnosis and management of Dravet syndrome: Recommendations from a North American Consensus Panel. *Pediatr Neurol*. 2017;68:18-34.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Antiepileptics – Nayzilam Prior Authorization Policy

- Nayzilam® (midazolam nasal spray – UCB, Inc.)

REVIEW DATE: 08/19/2020

OVERVIEW

Nayzilam is indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 12 years of age.[1]

Nayzilam is a benzodiazepine which is thought to work by the potentiation of gamma-aminobutyric acid (GABA)ergic neurotransmission resulting from binding at the benzodiazepine site of the $GABA_A$ receptor.[1] The recommended initial dose is one spray (5 mg dose) into one nostril. If needed, the recommended second dose is one additional 5 mg spray into the opposite nostril administered after 10 minutes if the patient has not responded to the initial dose. A second dose of Nayzilam should not be administered if the patient has trouble breathing or if there is excessive sedation that is uncharacteristic of the patient during a seizure cluster episode. No more than two doses of Nayzilam should be used to treat a single episode. It is recommended that Nayzilam be used to treat no more than one episode every 3 days and no more than five episodes per month. Nayzilam is available as a single-dose nasal spray unit containing 5 mg/0.1 mL of midazolam and supplied in boxes of two nasal spray units. Nayzilam is a Schedule C-IV controlled substance.

Disease Overview

Patients with epilepsy can experience acute repetitive seizures or seizure clusters.[2] The prevalence of epilepsy in the US is approximately 3.4 million people, and of these patients, an estimated 36% of patients have uncontrolled disease, a significant risk factor for seizure clusters.[3,4] Seizure clusters are estimated to occur in approximately 15% of adults with uncontrolled epilepsy.[5] No consensus definition of a seizure cluster has been agreed upon, and seizure cluster is not listed in the International League Against Epilepsy commission on classification and terminology.[2] A broad definition of seizure clusters has been proposed to be "acute episodes of deterioration in seizure control". More specifically, they could be defined as a series of grouped seizures that have short interictal periods. However, the number of seizures and the interictal period are the subject of controversy. Seizure clusters can result in increased emergency room visits or hospitalization, and they can disrupt the daily life, studies, and work of patients and caregivers. They are particularly concerning because of their association with status epilepticus, a potentially life-threatening condition. Benzodiazepine rescue medication is the primary acute therapy for management of seizure clusters, helping to abort clusters and reduce emergency department visits.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Nayzilam. Because of the specialized skills required for evaluation and diagnosis of patients treated with Nayzilam as well as the monitoring required for adverse events and efficacy, approval requires Nayzilam to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nayzilam is recommended in those who meet the following criteria:

FDA-Approved Indications

17. **Intermittent Episodes of Frequent Seizure Activity (i.e., seizure clusters, acute repetitive seizures).** Approve for 1 year if the patient meets the following criteria (A and B):
    - **A)** Patient is currently receiving maintenance antiepileptic medication(s); AND
    - **B)** Nayzilam is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nayzilam is not recommended in the following situations:

12. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

68. Nayzilam® nasal spray [prescribing information]. Plymouth, MN: Proximagen, LLC; May 2019.
69. Jafarpour S, Hirsch LJ, Gaínza-Lein M, et al. Seizure cluster: Definition, prevalence, consequences, and management. *Seizure*. 2019;68:9-15.
70. Zack M, Kobau R. National and state estimates of the numbers of adults and children with active epilepsy - United States, 2015. *MMWR Morb Mortal Wkly Rep*. 2017;66(31):821-825. Available at: https://www.cdc.gov/mmwr/volumes/66/wr/mm6631a1.htm. Accessed on August 17, 2020.
71. Chen B, Choi H, Hirsch LJ, et al. Prevalence and risk factors of seizure clusters in adult patients with epilepsy. *Epilepsy Res*. 2017;133:98-102.
72. Chen Z, Brodie MJ, Liew D, et al. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. *JAMA Neurol*. 2018;75(3):279-286.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/07/2019
Annual Revision	No change to criteria.	08/19/2020

PRIOR AUTHORIZATION POLICY

POLICY: Antiepileptics – Valtoco Prior Authorization Policy

- Valtoco® (diazepam nasal spray – Neurelis)

REVIEW DATE: 02/03/2021

OVERVIEW

Valtoco, a benzodiazepine, is indicated for the acute treatment of **intermittent, stereotypic episodes of frequent seizure activity** (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 6 years of age.[1]

Valtoco is for acute treatment only. Do not use more than two doses of Valtoco to treat a single episode.[1] It is recommended that Valtoco be used to treat no more than one episode every five days and no more than five episodes per month.

Disease Overview

Patients with epilepsy can experience acute repetitive seizures or seizure clusters.[2] Patients with severe and/or poorly controlled epilepsy are more likely to experience seizure clusters. Seizure clusters can result in increased emergency room visits or hospitalization, and they can disrupt the daily life, studies, and work of patients and caregivers. They are particularly concerning because of their association with status epilepticus, a potentially life-threatening condition. Benzodiazepine rescue medication is the primary acute therapy for management of seizure clusters, helping to abort clusters and reduce emergency department visits.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Valtoco. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Valtoco is recommended in those who meet the following criteria:

FDA-Approved Indications

18. **Intermittent Episodes of Frequent Seizure Activity (i.e., seizure clusters, acute repetitive seizures).** Approve for 1 year if the patient meets the following criteria (A and B):
    A) Patient is currently receiving maintenance antiepileptic medication(s); AND
    B) The medication is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Valtoco is not recommended in the following situations:

13. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

73. Valtoco® nasal spray [prescribing information]. San Diego, CA: Neurelis, Inc.; January 2020.
74. Jafarpour S, Hirsch LJ, Gaínza-Lein M, et al. Seizure cluster: Definition, prevalence, consequences, and management. *Seizure*. 2019;68:9-15.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	02/05/2020
Annual Revision	No criteria changes.	02/03/2021

PRIOR AUTHORIZATION POLICY

POLICY: Antiepileptics – Vigabatrin (Sabril) Prior Authorization Policy

- Sabril® (vigabatrin tablets and powder for solution – Lundbeck, generics)

REVIEW DATE: 09/16/2020

OVERVIEW

Vigabatrin is indicated for the following:[1]

- **Monotherapy for infantile spasms** in pediatric patients 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss. Vigabatrin is not indicated as a first line agent for complex partial seizures.
- **Adjunctive therapy for refractory complex partial seizures** in adults and pediatric patients ≥ 2 years of age who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss.

According to the vigabatrin prescribing information, use the lowest dosage and shortest exposure to vigabatrin consistent with clinical objectives.[1] For infantile spasms, vigabatrin is titrated to a maximum dose of 150 mg/kg/day given in two divided doses (75 mg/kg twice daily). Vigabatrin should be withdrawn if a substantial clinical benefit is not observed within 2 to 4 weeks. For refractory complex partial seizures, vigabatrin is titrated to 3,000 mg/day (1,500 mg twice daily) for patients ≥ 17 years of age and to 2,000 mg/day (1,000 mg twice daily) for pediatric patients 10 years to 16 years of age. In patients with refractory complex partial seizures, vigabatrin should be withdrawn if a substantial clinical benefit is not observed within 3 months of initiating treatment.

Safety

Vigabatrin has a Boxed Warning with regard to permanent vision loss.[1] In some cases, vigabatrin also can damage the central retina and may decrease visual acuity. The onset of vision loss from vigabatrin is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time after starting treatment, even after months or years. The risk of vision loss increases with increasing dose and cumulative exposure, but there is no dose or exposure known to be free of risk of vision loss. Vision assessment is recommended at baseline (no later than 4 weeks after starting vigabatrin), at least every 3 months during

therapy, and about 3 to 6 months after the discontinuation of therapy. Once detected, vision loss due to vigabatrin is not reversible. Because of the risk of vision loss, vigabatrin should be withdrawn from patients with refractory complex partial seizures who fail to show substantial clinical benefit within 3 months of initiation and within 2 to 4 weeks of initiation for patients with infantile spasms, or sooner if treatment failure becomes obvious. Because of the risk of permanent vision loss, vigabatrin is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Vigabatrin REMS Program.

Guidelines/Recommendations

In 2012 the American Academy of Neurology (AAN) and the Child Neurology Society updated the evidence-based guideline for the medical treatment of infantile spasms.[2] The guidelines note that low-dose adrenocorticotropic hormone (ACTH) is a first-line agent for the short-term treatment of infantile spasms. ACTH or vigabatrin may be useful for short-term treatment of infantile spasms, with ACTH considered preferentially over vigabatrin. Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to vigabatrin in infants with cryptogenic infantile spasms, to possibly improve developmental outcome. A shorter lag time to treatment of infantile spasms with either hormonal therapy or vigabatrin possibly improves long-term developmental outcomes. The Infantile Spasms Working Group (ISWG) published a US consensus report on infantile spasms in 2010.[3] Data regarding ACTH use and vigabatrin use in infantile spasms were detailed.[3] ACTH is an effective first-line therapy for infantile spasms. Vigabatrin is considered a drug of first choice for infantile spasms comorbid with tuberous sclerosis complex, and it is the drug of second or third choice for children with other symptomatic or cryptogenic infantile spasms.

The American Academy of Neurology (AAN) and the American Epilepsy Society published a guideline update for treatment-resistant epilspsy (2018) that clobazam is probably effective as add-on therapy for LGS and is possibly effective as add-on therapy for treatment-resistant adult focal epilepsy.[4] Vigabatrin is effective as add-on therapy in treatment-resistant adult focal epilepsy based on two Class I studies, but it should not be used as a first-line treatment. The benefits of vigabatrin should be weighed against the risks, particularly the risk of irreversible retinopathy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of vigabatrin. Because of the specialized skills required for evaluation and diagnosis of patients treated with vigabatrin as well as the monitoring required for adverse events and long-term efficacy, initial approval requires vigabatrin to be prescribed by, or in consultation with, a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of vigabatrin is recommended in those who meet the following criteria:

FDA-Approved Indications

11. Infantile Spasms. Approve for 6 months if the patient meets the following criteria (A, B, and C):
- **B)** Patient is ≤ 2 years of age; AND
- **C)** Vigabatrin is being used as monotherapy; AND
- **D)** The medication is prescribed by, or in consultation with, a neurologist.

12. Treatment-Refractory Complex Partial Seizures. Approve for the duration noted below if the patient meets ONE of the following criteria (A or B):

G) Initial Therapy: Approve for 3 months if the patient meets the following criteria (i, ii, and iii):

i. Patient is ≥ 2 years of age; AND

ii. Patient has tried and/or is concomitantly receiving at least three other antiepileptic drugs; AND

Note: Examples of antiepileptic drugs include valproic acid, gabapentin, phenytoin, carbamazepine, oxcarbazepine, lacosamide, levetiracetam, zonisamide, Fycompa (perampanel tablet or oral suspension), lamotrigine, topiramate, rufinamide, tiagabine, felbamate, Diacomit (stiripentol capsules or oral suspension), and clobazam.

iii. The medication is prescribed by, or in consultation with, a neurologist.

H) Patient is Currently Receiving Vigabatrin: Approve for 1 year if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of vigabatrin is not recommended in the following situations:

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

122. Sabril® tablets and oral solution [prescribing information]. Deerfield, IL: Lundbeck; January 2020.
123. Go CY, Mackay MT, Weiss SK, et al. Evidence-based guideline update: medical treatment of infantile spasms: Report of the guideline development subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2012;78:1974-1980.
124. Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: a US consensus report. *Epilepsia*. 2010;51(10):2175-2189.
125. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2018;91:82-90.
126. Treiman DM. Management of refractory complex partial seizures: current state of the art. *Neuropsychiatr Dis Treat*. 2010;6:297-308.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	09/18/2019
Selected Revision	For the approval condition of treatment-refractory complex partial seizures, the age criterion was changed from ≥ 10 years of age to ≥ 2 years of age based on a change to the approved indication.	03/25/2020
Annual Revision	No change to criteria.	09/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Antifungal – Cresemba® (isavuconazonium sulfate capsules – Astellas Pharma)

DATE REVIEWED: 06/10/2020

OVERVIEW

Cresemba, an azole antifungal, is indicated for use in patients ≥ 18 years of age for the treatment of invasive aspergillosis or invasive mucormycosis.[1] Cresemba is also available for use as an intravenous (IV) infusion. Switching between the IV and oral formulations is acceptable as the two formulations are bioequivalent.

In the pivotal study involving patients with invasive aspergillosis, patients were initiated on IV Cresemba before transitioning to oral Cresemba therapy.[1] The mean treatment duration was 47 days, of which patients received IV Cresemba for 8 to 9 days. In an open-label, non-comparative study that included a subset of patients with invasive mucormycosis, patients were treated with either IV or oral Cresemba. The median duration of Cresemba therapy was 102 days.

Guidelines/Recommendations

The Infectious Diseases Society of America (IDSA) [2016] recommends Cresemba as a treatment option for invasive aspergillosis and different invasive syndromes of *Aspergillus* (e.g., invasive pulmonary aspergillosis, invasive sinus aspergillosis, aspergillosis of the central nervous system, etc).[2] Treatment of invasive aspergillosis should be continued for a minimum of 6 to 12 weeks, depending on the degree and duration of immunosuppression, site of disease, and evidence of disease improvement.

The European Conference on Infections in Leukemia (ECIL), a collaboration between the European Organization for Research and Treatment of Cancer (EORTC), the European Society for Bone and Marrow Transplantation (EBMT), the European Leukemia Net (ELN), and the International Immunocompromised Host Society (CSH), provided recommendations for the treatment of several types of fungal infections, including invasive aspergillosis and mucormycosis in hematologic patients (2016).[3] The ECIL-6 recommendations list Cresemba, among other antifungals, as first-line for the treatment of invasive aspergillosis (A1 grade; good evidence from at least one properly randomized, controlled trial). The panel recommends a multidisciplinary approach, including antifungal therapy (amphotericin B), surgery, and control of the underlying conditions (e.g., control of diabetes, use of hematopoietic growth factor if the patient is neutropenic, discontinuation/tapering of steroids, reduction of immunosuppressive therapy).

The European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and the European Confederation of Medical Mycology (ECMM) published joint clinical guidelines for the management of mucormycosis in 2013.[4] The panel notes that there are no published, well-designed, randomized clinical efficacy trials in the field of mucormycosis. Surgery, whenever possible, is strongly recommended to be combined with medical treatment. The drug of choice for the treatment of invasive mucormycosis is liposomal amphotericin B.

The National Comprehensive Cancer Network (NCCN) Prevention and Treatment of Cancer-Related Infections clinical guidelines (version 2.2020 – June 5, 2020) note that Cresemba is currently not recommended for use as prophylaxis against fungal infections in patients with cancer and neutropenia.[5]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Cresemba capsules.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cresemba is recommended in those who meet the following criteria:

FDA-Approved Indications

1. ***Aspergillus* Infections – Treatment.** Approve for 3 months.

2. **Mucormycosis – Treatment.** Approve for 3 months.

Other Uses with Supportive Evidence

3. **Fungal Infections (Systemic) That Are Susceptible to Cresemba – Treatment.** Approve for 3 months.

4. **Patients Currently Receiving Intravenous Cresemba or Oral Cresemba Capsules.** Approve for 3 months to complete the course of therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Cresemba has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

30. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

43. Cresemba® capsules [prescribing information]. Northbrook, IL: Astellas Pharma US, Inc.; December 2019.
44. Patterson TF, Thompson GR, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;63(4):e1-e60.
45. Tissot F, Agrawal S, Pagano L, et al. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis, and mucormycosis in leukemia and hematopoietic stem cell transplant patients. *Haematologica*. 2017;102(3):433-444.
46. Cornely OA, Arikan-Akdagli S, Dannaoui E, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. *Clin Microbiol Infect*. 2014;20(Suppl 3):5-26.
47. The NCCN Prevention and Treatment of Cancer-Related Infections Clinical Practice Guidelines in Oncology (version 2.2020 –June 5, 2020). ©2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 5, 2020.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	06/05/2019
Annual revision	No criteria changes	06/10/2020

PRIOR AUTHORIZATION POLICY

POLICY: Antifungal – Noxafil® (posaconazole delayed-release tablets [generics] and oral suspension – Merck)

DATE REVIEWED: 06/10/2020

OVERVIEW

Noxafil, an azole antifungal, is indicated for prophylaxis of invasive *Aspergillus* and *Candida* infections in patients who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy.[1] Noxafil oral suspension is also indicated for the treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole. Noxafil delayed-release tablets and oral suspension are indicated for use in patients ≥ 13 years of age. The delayed-release tablets and oral suspension should not be used interchangeably.

The duration of Noxafil therapy is varied. In a pivotal study, where Noxafil oral suspension was compared with fluconazole capsules as prophylaxis for the prevention of invasive fungal infections in allogeneic HSCT recipients with GVHD, the mean duration of Noxafil therapy was 80 days.[1]

Guidelines/Recommendations

The Infectious Diseases Society of America (IDSA) guidelines for aspergillosis (2016) recommend Noxafil for prophylaxis of invasive aspergillosis.[2] The IDSA guidelines for candidiasis (2016) notes Noxafil as one of the drugs of choice for the treatment of fluconazole-refractory oropharyngeal candidiasis.[3] The National Comprehensive Cancer Network (NCCN) Guidelines for the Prevention and Treatment of Cancer-Related Infections (version 2.2020 – June 5, 2020) recommends Noxafil (category 1) for antifungal prophylaxis in patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) and neutropenia who are receiving induction or re-induction chemotherapy; voriconazole is a category 2B recommendation.[4] The IDSA notes Noxafil as having high-quality evidence for prophylaxis of candidiasis, whereas voriconazole is noted as having moderate-quality evidence.

Other Uses

The IDSA guidelines for aspergillosis (2016) list Noxafil as an option for treatment of invasive aspergillosis that is refractory to other antifungal therapies or that has progressed despite treatment.[2] The guidelines for prevention and treatment of opportunistic infections in adults and adolescents with human immunodeficiency virus (HIV) infections (2019) note Noxafil as an option for treatment of patients with coccidiodomycosis.[4] The NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections (version 2.2020 – June5, 2020) include Noxafil as one of the antifungal therapies for the following: treatment of mouth and esophageal infections (e.g., oral thrush) refractory to fluconazole; invasive fusariosis; *Scedosporium* infections; and maintenance treatment of mucormycosis.[5] Additionally, the NCCN notes Noxafil as one of the antifungal therapies that are recommended for use as prophylaxis against fungal infections in patients with cancer (e.g., patients with AML or MDS; patients with graft-versus-host disease [GVHD]; hematopoietic cell transplant [HCT] recipients). Antifungal prophylaxis should be continued until resolution of neutropenia or GVHD. Noxafil is active against *Candida* and *Aspergillus* species, some *Zygomycetes* species; and against dimorphic fungi.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Noxafil delayed-release tablets and oral suspension.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Noxafil is recommended in those who meet the following criteria:

FDA-Approved Indications

5. ***Aspergillus* Infections – Prophylaxis.** Approve for 6 months.

6. ***Candida* Infections (Systemic) – Prophylaxis.** Approve for 6 months.

7. **Oropharyngeal candidiasis – Treatment.** Approve for 3 months.

Other Uses with Supportive Evidence

8. ***Aspergillus* Infections – Treatment.** Approve for 3 months.

9. **Mouth and Esophageal Infections (Refractory to Other Azole Antifungals) – Treatment.** Approve for 3 months.

10. **Mucormycosis – Maintenance.** Approve for 6 months.

11. **Fusariosis, Invasive – Treatment.** Approve for 3 months.

12. ***Scedosporium* infections – Treatment.** Approve for 3 months.

13. **Fungal Infections (Systemic) In Patients with Human Immunodeficiency Virus (HIV) Infections (e.g., Histoplasmosis, Coccidioidomycosis) – Treatment.** Approve for 3 months.

14. **Fungal Infections (Systemic) In Patients At Risk Of Neutropenia – Prophylaxis.** Approve for 6 months.

15. **Fungal Infections (Systemic) That Are Susceptible to Noxafil – Treatment.** Approve for 3 months.

16. **Patients Currently Receiving Intravenous Noxafil or Oral Noxafil (Tablets or Oral Suspension).** Approve for 3 months to complete the course of therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Noxafil has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

31. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

48. Noxafil® delayed-release tablets and oral suspension [prescribing information]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.; March 2020.
49. Patterson TF, Thompson GR, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2016;63(4):e1-e60.

50. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guidelines for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62(4):e1-50.
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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	06/05/2019
Annual revision	No criteria changes.	06/10/2020

PRIOR AUTHORIZATION WITH STEP THERAPY POLICY

POLICY: Tolsura™ (itraconazole capsules – Mayne Pharma)

DATE REVIEWED: 06/10/2020

OVERVIEW

Tolsura, a branded itraconazole product, is indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised adult patients: blastomycosis (pulmonary and extrapulmonary); histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis; and aspergillosis (pulmonary and extrapulmonary) in patients who are intolerant of or who are refractory to amphotericin B therapy.[1] Limitations of use: Tolsura is not indicated for the treatment of onychomycosis. Tolsura is not interchangeable or substitutable with other itraconazole products due to the differences in the dosing between Tolsura and other itraconazole products. Compared with itraconazole capsules, the bioavailability of Tolsura is greater (relative bioavailability is 173% with 21% less variability).[2] The recommended dose for the treatment of blastomycosis or histoplasmosis is 130 mg (2 x 65 mg capsules) once daily (QD). The dose is 130 mg (2 x 65 mg capsules) QD or twice daily (BID) for the treatment of aspergillosis.[1] A loading dose of 130 mg (2 x 65 mg capsules) three times a day (TID) may be necessary for the treatment of life-threatening infections. Tolsura is available as 65 mg capsules.

Itraconazole capsule (Sporanox, generics) is indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised patients: blastomycosis (pulmonary and extrapulmonary); histoplasmosis (including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis); and aspergillosis (pulmonary and extrapulmonary) in patients who are intolerant of or who are refractory to amphotericin B therapy.[3] Itraconazole capsule is also indicated for the treatment of the following fungal infections in non-immunocompromised patients: onychomycosis of the toenail, with or without fingernail involvement, due to dermatophytes (tinea unguium); and onychomycosis of the fingernail due to dermatophytes (tinea unguium). The dose of itraconazole capsule (100 mg capsules) for the treatment of systemic fungal infections and onychomycosis range from 200 mg/day to 400 mg/day; a 600 mg/day loading dose (for 3 days) is recommended for life-threatening infections.

Itraconazole oral solution (Sporanox, generics) is indicated for the treatment of oropharyngeal and esophageal candidiasis.[4] The prescribing information notes that itraconazole oral solution was not

investigated in severely neutropenic patients with oropharyngeal and/or esophageal candidiasis and it is not recommended for initiation of treatment in patients at immediate risk of systemic candidiasis. The recommended dose of itraconazole oral solution (10 mg/mL) range from 100 mg (10 mL) to 200 mg (20 mL) per day. Itraconazole oral solution should not be used interchangeably with itraconazole capsule. Drug exposure is greater with the oral solution than with the capsules when the same dose of drug is given. Although itraconazole oral solution is not FDA-approved for the treatment of systemic fungal infections, both the capsule and liquid formulation of itraconazole are listed as options for use in the treatment and prophylaxis of systemic fungal infections by the Infectious Diseases Society of America (IDSA), American Thoracic Society (ATS) and the National Comprehensive Cancer Network (NCCN).[5-7] Many guidelines note improved bioavailability of the oral solution compared with the capsule formulation.[5,8,9] Therapeutic drug monitoring of itraconazole is recommended.

Clinical Efficacy/Guidelines

Tolsura has not yet been incorporated into guidelines. Conventional itraconazole (capsule and/or oral solution) is a treatment option for systemic fungal infections, including invasive aspergillosis, blastomycosis, and histoplasmosis.[5,6,10]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Tolsura. This Prior Authorization Policy also contains a Step Therapy component. When clinically appropriate, patients are directed to try one Preferred Step 1 agent (itraconazole capsules or oral solution) prior to Tolsura (Step 2). All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tolsura is recommended in those who meet the following criteria:

FDA-Approved Indications

13. **Blastomycosis – Pulmonary Or Extrapulmonary – Treatment.** Approve for 3 months if the patient meets one of the following criteria (A or B):
    - **a)** The patient has tried one of itraconazole capsules or oral solution; OR
    - **b)** The patient is currently receiving Tolsura for this condition.

14. **Histoplasmosis (Including Chronic Cavitary Pulmonary Disease and Disseminated, Non-Meningeal) – Treatment.** Approve for 3 months if the patient meets one of the following criteria (A or B):
    - **a)** The patient has tried one of itraconazole capsules or oral solution; OR
    - **b)** The patient is currently receiving Tolsura for this condition.

15. **Aspergillosis – Pulmonary Or Extrapulmonary – Treatment.** Approve for 3 months if the patient meets one of the following criteria (A or B):
    - **a)** The patient has tried one of itraconazole capsules or oral solution; OR
    - **b)** The patient is currently receiving Tolsura for this condition.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Tolsura not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for

these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

32. Onychomycosis. Treatment of onychomycosis is noted as a Limitation of Use in the prescribing information.

33. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

53. Tolsura capsule [prescribing information]. Greenville, SC: Mayne Pharma; December 2018.
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55. Sporanox® capsule [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; March 2019.
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57. Patterson TF, Thompson GR, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2016;63(4):e1-e60.
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59. The NCCN Prevention and Treatment of Cancer-Related Infections Clinical Practice Guidelines in Oncology (version2.2020 – June 5, 2020). ©2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 5, 2020.
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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	06/05/2019
Annual revision	No criteria changes	06/10/2020

PRIOR AUTHORIZATION POLICY

POLICY: Antifungals – Voriconazole tablets and oral suspension (Vfend® – Roerig, a division of Pfizer; generics)

DATE REVIEWED: 06/10/2020

OVERVIEW

Voriconazole (Vfend, generics), an azole antifungal, is indicated in adults and pediatric patients (≥ 2 years of age) for the treatment of invasive aspergillosis, esophageal candidiasis, and for the treatment of serious fungal infections caused by *Scedosporium apiospermum* (asexual form of *Pseudallescheria boydii*) and *Fusarium* spp., including *Fusarium solani* in patients intolerant of, or refractory to, other therapy.[1] Voriconazole is also indicated for the treatment of candidemia in non-neutropenic patients and the

following *Candida* infections: disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds. The duration of voriconazole therapy is varied, ranging from a median duration of 15 days for esophageal candidiasis to 76 days for invasive aspergillosis.

Guidelines/Recommendations

The Infectious Diseases Society of America (IDSA) recommends Voriconazole as a treatment option for invasive aspergillosis (2016) and different invasive syndromes of *Aspergillus* (e.g., invasive pulmonary aspergillosis, invasive sinus aspergillosis, aspergillosis of the central nervous system) and for candidemia and candidiasis (2016).[2,3] The National Comprehensive Cancer Network (NCCN) Guidelines for Prevention and Treatment of Cancer-Related Infections (version 2.2020 – June 5, 2020) note Voriconazole as an option for the treatment of infections caused by *Fusarium* and *Scedosporium* species.[4]

Other Uses

The IDSA guidelines for aspergillosis (2016) recommend Voriconazole for prophylaxis of invasive aspergillosis. The IDSA guidelines for management of candidiasis (2016) note voriconazole as a treatment option for the following infections: *Candida* intravascular infections, including endocarditis and infections of implantable cardiac devices; fluconazole-refractory oropharyngeal candidiasis; *Candida* endophthalmitis.[3] The IDSA guidelines for the management of blastomycosis (2008) note Voriconazole as an option for the treatment of central nervous system blastomycosis.[5] The NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections (version 2.2020 – June 5, 2020) note Voriconazole as an option for prophylactic use against fungal infections in patients at risk of neutropenia (e.g., patients with cancer; patients with graft-versus-host disease [GVHD]; hematopoietic cell transplant [HCT] recipients).[4] Antifungal prophylaxis should be continued until resolution of neutropenia or GVHD; in one study involving HCT recipients, Voriconazole was used for up to 6 months. The guidelines for prevention and treatment of opportunistic infections in adults and adolescents with human immunodeficiency virus (HIV) infections (2019) recommend voriconazole for prophylaxis or chronic suppressive/maintenance treatment for various fungal infections in patients with HIV (e.g., histoplasmosis, coccidioidomycosis, infections caused by *Talaromyces marneffei* [formerly known as *Penicillium marneffei]*).[6]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Vfend tablets and oral suspension and generic voriconazole tablets and oral suspension.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Voriconazole is recommended in those who meet the following criteria:

FDA-Approved Indications

17. ***Aspergillus* Infections – Treatment.** Approve for 3 months if the patient meets one of the following criteria (A or B):
    a. Generic voriconazole tablets or oral suspension is requested; OR
    b. If brand Vfend tablet or brand Vfend oral suspension is requested, the patient has tried the corresponding generic voriconazole product (tablet or oral suspension) AND cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product,

which per the prescribing physician, would result in a significant allergy or serious adverse reaction.

18. Esophageal Candidiasis – Treatment. Approve for 3 months if the patient meets one of the following criteria (A or B):
   a. Generic voriconazole tablets or oral suspension is requested; OR
   b. If brand Vfend tablet or brand Vfend oral suspension is requested, the patient has tried the corresponding generic voriconazole product (tablet or oral suspension) AND cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescribing physician, would result in a significant allergy or serious adverse reaction.

19. Infections caused by *Scedosporium apiospermum* – Treatment. Approve for 3 months if the patient meets one of the following criteria (A or B):
   a. Generic voriconazole tablets or oral suspension is requested; OR
   b. If brand Vfend tablet or brand Vfend oral suspension is requested, the patient has tried the corresponding generic voriconazole product (tablet or oral suspension) AND cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescribing physician, would result in a significant allergy or serious adverse reaction.

20. Infections caused by *Fusarium* species – Treatment. Approve for 3 months if the patient meets one of the following criteria (A or B):
   a. Generic voriconazole tablets or oral suspension is requested; OR
   b. If brand Vfend tablet or brand Vfend oral suspension is requested, the patient has tried the corresponding generic voriconazole product (tablet or oral suspension) AND cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescribing physician, would result in a significant allergy or serious adverse reaction.

21. *Candida* (Systemic) Infections – Treatment. Approve for 3 months if the patient meets one of the following criteria (A or B):
   a. Generic voriconazole tablets or oral suspension is requested; OR
   b. If brand Vfend tablet or brand Vfend oral suspension is requested, the patient has tried the corresponding generic voriconazole product (tablet or oral suspension) AND cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescribing physician, would result in a significant allergy or serious adverse reaction.

Other Uses with Supportive Evidence

22. *Aspergillus* Infections – Prophylaxis. Approve for 6 months if the patient meets one of the following criteria (A or B):
   A) Generic voriconazole tablets or oral suspension is requested; OR
   B) If brand Vfend tablet or brand Vfend oral suspension is requested, the patient has tried the corresponding generic voriconazole product (tablet or oral suspension) AND cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g.,

difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescribing physician, would result in a significant allergy or serious adverse reaction.

23. **Oropharyngeal Candidiasis (fluconazole-refractory) – Treatment.** Approve for 3 months if the patient meets one of the following criteria (A or B):
    A) Generic voriconazole tablets or oral suspension is requested; OR
    B) If brand Vfend tablet or brand Vfend oral suspension is requested, the patient has tried the corresponding generic voriconazole product (tablet or oral suspension) AND cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescribing physician, would result in a significant allergy or serious adverse reaction.

24. ***Candidia* endophthalmitis – Treatment.** Approve for 3 months if the patient meets one of the following criteria (A or B):
    A) Generic voriconazole tablets or oral suspension is requested; OR
    B) If brand Vfend tablet or brand Vfend oral suspension is requested, the patient has tried the corresponding generic voriconazole product (tablet or oral suspension) AND cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescribing physician, would result in a significant allergy or serious adverse reaction.

25. **Blastomycosis – Treatment.** Approve for 3 months if the patient meets one of the following criteria (A or B):
    a. Generic voriconazole tablets or oral suspension is requested; OR
    b. If brand Vfend tablet or brand Vfend oral suspension is requested, the patient has tried the corresponding generic voriconazole product (tablet or oral suspension) AND cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescribing physician, would result in a significant allergy or serious adverse reaction.

26. **Fungal Infections (Systemic) in Patients At Risk Of Neutropenia – Prophylaxis.** Approve for 6 months if the patient meets one of the following criteria (A or B):
    A) Generic voriconazole tablets or oral suspension is requested; OR
    B) If brand Vfend tablet or brand Vfend oral suspension is requested, the patient has tried the corresponding generic voriconazole product (tablet or oral suspension) AND cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescribing physician, would result in a significant allergy or serious adverse reaction.

27. **Fungal Infections (Systemic) In Patients with Human Immunodeficiency Virus (HIV) – Prophylaxis or Treatment.** Approve for 6 months if the patient meets one of the following criteria (A or B):
    A) Generic voriconazole tablets or oral suspension is requested; OR
    B) If brand Vfend tablet or brand Vfend oral suspension is requested, the patient has tried the corresponding generic voriconazole product (tablet or oral suspension) AND cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g.,

difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescribing physician, would result in a significant allergy or serious adverse reaction.

12. Fungal Infections (Systemic) That Are Susceptible to Voriconazole – Treatment. Approve for 3 months if the patient meets one of the following criteria (A or B):

A) Generic voriconazole tablets or oral suspension is requested; OR

B) If brand Vfend tablet or brand Vfend oral suspension is requested, the patient has tried the corresponding generic voriconazole product (tablet or oral suspension) AND cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescribing physician, would result in a significant allergy or serious adverse reaction.

13. Patients Currently Receiving Intravenous Voriconazole or Oral Voriconazole (Tablets or Oral Suspension). Approve for 3 months to complete the course of therapy if the patient meets ONE of the following criteria (A or B):

A) Generic voriconazole tablets or oral suspension is requested; OR

B) If brand Vfend tablet or brand Vfend oral suspension is requested, the patient has tried the corresponding generic voriconazole product (tablet or oral suspension) AND cannot take the generic voriconazole product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product, which per the prescribing physician, would result in a significant allergy or serious adverse reaction.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Voriconazole has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

34. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	06/05/2019
Update	08/27/19: Changed policy name from "Antifungals – Voriconazole (Vfend) [Oral] PA Policy" to "Antifungals – Voriconazole Tablets and Oral Suspension PA Policy".	--
Annual revision	No criteria changes.	06/10/2020

PRIOR AUTHORIZATION POLICY

POLICY: Antifungals (Azoles) – Intravenous Products Prior Authorization Policy

- Cresemba® (isavuconazonium sulfate injection for intravenous infusion – Astellas)
- Fluconazole injection for intravenous infusion – generic only
- Noxafil® (posaconazole injection for intravenous infusion injection – Merck)
- Vfend® (voriconazole injection for intravenous infusion use – Pfizer, generic)

REVIEW DATE: 02/10/2021

OVERVIEW

Cresemba injection for intravenous (IV) infusion, fluconazole injection for IV infusion, Noxafil injection for IV infusion, and voriconazole injection for IV infusion are azole antifungals. These products are indicated for prophylaxis and/or treatment of fungal infections, including *Candida* infections, cryptococcal meningitis, esophageal candidiasis, invasive aspergillosis, and invasive mucormycosis.[1-4]

Injectable formulations of some antifungals have been compounded with other topical products (clindamycin, clotrimazole, ketoconazole, and mupirocin) to make foot baths and other products. There are no data to support these uses.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cresemba injection for intravenous (IV) infusion, fluconazole injection for IV infusion, Noxafil injection for IV infusion, and voriconazole injection for IV infusion, when these products are prescribed in conjunction with select topical products: clindamycin, clotrimazole, ketoconazole, and mupirocin. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: If there are no prescription claims for topical clindamycin, topical clotrimazole, topical ketoconazole, and/or topical mupirocin products in the past 180 days, the Prior Authorization edit will not be applied in adjudication. Prior Authorization will only apply to prescriptions for Cresemba injection for IV infusion, fluconazole injection for IV infusion, Noxafil injection for IV infusion, and voriconazole injection for IV infusion when there is history of topical clindamycin, topical clotrimazole, topical ketoconazole, and/or topical mupirocin products in the past 180 days.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cresemba injection for intravenous (IV) infusion, fluconazole injection for IV infusion, Noxafil injection for IV infusion, and voriconazole injection for IV infusion is recommended in those who meet the following criteria:

FDA-Approved Indications

16. Systemic Fungal Infections (Prophylaxis or Treatment). Approve for 3 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cresemba injection for intravenous (IV) infusion, fluconazole injection for IV infusion, Noxafil injection for IV infusion, and voriconazole injection for IV infusion is not recommended in the following situations:

35. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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70. Fluconazole in sodium chloride, USP [prescribing information]. Schaumburg, IL: Sagent Pharmaceuticals.; July 2019.
71. Noxafil® injection for intravenous use, delayed-release tablets for oral use, oral suspension [prescribing information]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp, a subsidiary of Merck & Co., Inc.; September 2017.
72. Vfend® lyophilized powder for injection [prescribing information]. New York, NY: Roerig, Division of Pfizer; January 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	02/06/2019
Update	Clarified indications for oral/injectable Noxafil and oral/injectable voriconazole.	04/17/2019
Selected Revision	Added to the list of products that will trigger the PA policy: topical clotrimazole products (cream or solution), topical ketoconazole products (cream, foam, or gel), and topical mupirocin products (cream or ointment). Previously, only topical clindamycin products were listed in the policy.	7/31/2019
Update	9/12/2019: Removed the formulations within the parentheses (Policy Statement and Automation): topical clindamycin products (gel, lotion, solution), topical clotrimazole products (cream or solution), topical ketoconazole products (cream, foam, or gel), and topical mupirocin products (cream or ointment) such that the specific formulations are not listed. Revised wording: topical clindamycin products, topical clotrimazole products, topical ketoconazole products, and topical mupirocin products.	--
Annual Revision	No criteria changes.	02/12/2020
Annual Revision	• Slight wording changes: o **Policy statement:** Revised "… when these products are prescribed in conjunction with topical clindamycin products, topical clotrimazole products, topical ketoconazole products, and/or topical mupirocin products" to "… when these products are prescribed in conjunction with select topical products: clindamycin, clotrimazole, ketoconazole, and mupirocin". o **Automation:** Revised "Prior Authorization will only apply to IV Cresemba, fluconazole, Noxafil, and voriconazole with history of topical clindamycin products, topical clotrimazole products, topical ketoconazole products, and/or topical mupirocin products in the past 180 days." to "Prior Authorization will only apply to prescriptions for Cresemba injection for intravenous (IV) infusion, fluconazole injection for IV infusion, Noxafil injection for IV infusion, and voriconazole injection for IV infusion when there is history of topical clindamycin, topical clotrimazole, topical ketoconazole, and/or topical mupirocin products in the past 180 days". • No criteria changes.	02/10/2021

PRIOR AUTHORIZATION POLICY

POLICY: Antiparasitics – Impavido® (miltefosine capsules – Profounda, Inc.)

DATE REVIEWED: 04/22/2020

OVERVIEW

Impavido is indicated in adults and adolescents ≥ 12 years of age weighing ≥ 30 kg for the treatment of visceral leishmaniasis caused by *Leishmania donovani*; cutaneous leishmaniasis caused by *L. braziliensis*, *L. guyanensis*, and *L. panamensis*; and mucosal leishmaniasis caused by *L. braziliensis*.[1] Limitation of use: *Leishmania* species studied in clinical trials evaluating Impavido were based on epidemiologic data; there may be geographic variation in clinical response of the same *Leishmania* species to Impavido; and the efficacy of Impavido in the treatment of other *Leishmania* species has not been evaluated.

Impavido is active *in vitro* against promastigotes and amastigotes of a variety of *Leishmania* species and anti-leishmanial activity has been demonstrated in clinical infections.[1] The exact mechanism of action is unknown. The recommended dose of Impavido is one 50 mg capsule twice daily with food for patients who weigh between 30 kg and 44 kg, and one 50 mg capsule three times a day with food for patients who weigh ≥ 45 kg. The treatment duration is 28 consecutive days.

A systematic review of four studies conducted in the Americas evaluated the efficacy of Impavido in pediatric patients ≤ 12 years of age with cutaneous leishmaniasis (n = 130).[2] The regimen was similar for all studies, with a target dose of 2.5 mg/kg/day (given as three times a day) for 28 days. The reported efficacy ranged from 63.1% to 82.8%.

Disease Overview

Leishmaniasis is a vector-borne disease that is transmitted by sandflies.[3] The number of annual new cases of leishmaniasis is unknown; it is estimated there are 700,000 to 1 million new cases annually. The cases of leishmaniasis in the US reflect travel and immigration patterns; leishmaniasis is not endemic to the US.[4] There are three primary forms of leishmaniasis: cutaneous, mucosal, and visceral.[3-5] Cutaneous leishmaniasis is the most common form, both in general and in US travelers. Mucosal leishmaniasis is the least common form of the three and it can be a sequela of cutaneous leishmaniasis, resulting from dissemination of the parasites from the skin to the naso-oropharyngeal mucosa.[4] Visceral leishmaniasis can affect several internal organs (usually the spleen, liver, and bone marrow) and can be life-threatening. If left untreated, visceral leishmaniasis can become fatal, either directly from the disease or indirectly from complications such as secondary bacterial infection or hemorrhage.[3,4]

Guidelines/Recommendations

In March 2011, Impavido was added to the World Health Organization (WHO) Essential Medicines List as an anti-leishmanial medicine.[6] The current WHO recommendations for the treatment of leishmaniasis include Impavido, liposomal amphotericin B, amphotericin B deoxycholate, paromomycin (not available in the US), pentavalent antimonial compounds (not available in the US) with or without pentoxifylline, systemic azole therapies, and thermotherapy.[6,7]

The Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH) released guidelines for the management of persons with leishmaniasis in 2016.[8] Systemic therapies, including Impavido, are recommended for the treatment of patients with cutaneous, mucosal, or visceral leishmaniasis.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Impavido. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Impavido as well as the monitoring required for adverse events and long-term efficacy, approval

requires Impavido to be prescribed by, or in consultation with, a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Impavido is recommended in those who meet the following criteria:

FDA-Approved Indications

28. Leishmaniasis, Visceral, Cutaneous, or Mucosal. Approve Impavido for 1 month if prescribed by, or in consultation with, an infectious diseases specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Impavido has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

36. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/10/2019
Annual Revision	No criteria changes	04/22/2020

PRIOR AUTHORIZATION POLICY

POLICY: Attention Deficit Hyperactivity Disorder Non-Stimulant Medications Prior Authorization Policy

- Intuniv® (guanfacine extended-release tablets – Shire Pharmaceuticals, generics)
- Kapvay® (clonidine hydrochloride extended-release tablets – Concordia, generics)
- Strattera® (atomoxetine capsules – Eli Lilly and Company, generics)

REVIEW DATE: 08/05/2020

OVERVIEW

Currently, there are three non-stimulant medications approved for the treatment of attention deficit hyperactivity disorder (ADHD): atomoxetine (Strattera, generics), guanfacine extended-release tablets (Intuniv, generics), and clonidine extended-release tablets (Kapvay, generics).[1-3] Atomoxetine, a selective norepinephrine reuptake inhibitor, is indicated for the treatment of ADHD in children ≥ 6 years of age, adolescents, and adults.[1] Guanfacine extended-release tablets and clonidine extended-release tablets, both of which are alpha agonists, are approved for use in children and adolescents aged 6 to 17 years with ADHD.[2,3] Guanfacine extended-release tablets and clonidine extended-release tablets are indicated for use as monotherapy or as adjunctive therapy to stimulant medications.

Clinical Efficacy

Patients with pervasive developmental disorders who have symptoms of ADHD respond to ADHD medications at a reduced rate compared with typically developing peers and often with undesirable side effects.[4,5] However, there is evidence to support use of these agents (e.g., stimulants, atomoxetine, guanfacine extended-release tablets, clonidine extended-release tablets) in this patient population.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of atomoxetine (Strattera, generics), guanfacine extended-release tablets (Intuniv, generics), and clonidine extended-release tablets (Kapvay, generics). All approvals are provided for the duration noted below.

Automation: An age edit targeting patients < 6 or > 18 years of age is recommended. Therefore, patients between the ages of 6 and 18 years will be approved at the point-of-service. For patients < 6 or > 18 years of age, coverage will be determined by Prior Authorization criteria.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of atomoxetine (Strattera, generics), guanfacine extended-release tablets (Intuniv, generics), or clonidine extended-release tablets (Kapvay, generics) is recommended in those who meet the following criteria:

FDA-Approved Indications

6. Attention Deficit Hyperactivity Disorder. Approve for 3 years if the patient is ≥ 6 years of age.

Other Uses with Supportive Evidence

7. **Pervasive Developmental Disorders (e.g., autism spectrum disorder, Asperger's disorder).** Approve for 3 years in patients with symptoms of attention deficit hyperactivity disorder (e.g., inattention, hyperactivity).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of atomoxetine (Strattera, generics), guanfacine extended-release tablets (Intuniv, generics), or clonidine extended-release tablets (Kapvay, generics) is not recommended in the following situations:

37. **Binge-Eating Disorder.** In one 10-week, placebo-controlled study in outpatients with binge-eating disorder (n = 40), atomoxetine was associated with a significantly greater reduction in binge-eating episode frequency vs. placebo.[6] Additional studies with atomoxetine are needed. There are no data with guanfacine extended-release tablets or clonidine extended-release tablets.

38. **Depression Without Attention Deficit/Hyperactivity Disorder.** Limited information is available on the use of atomoxetine for the treatment of major depressive disorder. In three case reports and one case series in 15 patients with depressive disorders, adding atomoxetine to a selective serotonin reuptake inhibitor (SSRI) resulted in further improvement.[7,8] However, in a published controlled trial, patients with major depressive disorder (without ADHD) [n =276] were treated with sertraline at doses up to 200 mg/day.[9] Patients who continued to experience depressive symptoms (n = 146) were then randomly assigned to either treatment with atomoxetine 40 to 120 mg/day or placebo for an additional 8 weeks. There was no difference between the atomoxetine/sertraline and placebo/sertraline treatment groups in mean change in depressive symptom severity or in the number of patients whose depressive symptoms remitted (40.3% vs. 37.8%, respectively; P = 0.865). Atomoxetine did not improve clinically significant depression in patients with Parkinson disease (n = 55) in one study.[10] There are no data with guanfacine extended-release tablets or clonidine extended-release tablets.

39. **Fibromyalgia.** In case reports, atomoxetine was effective in reducing fatigue and pain in fibromyalgia syndrome.[11] Well-controlled trials with atomoxetine are needed to establish safety and efficacy. There are no data with guanfacine extended-release tablets or clonidine extended-release tablets.

40. **Improve Cognitive Function (or Neuroenhancement).** The use of prescription medication to augment cognitive or affective function in otherwise healthy individuals (also known as neuroenhancement) is increasing in adult and pediatric populations.[19] A 2013 Ethics, Law, and Humanities Committee position paper, endorsed by the American Academy of Neurology (AAN) indicates that based on currently available data and the balance of ethics issues, neuroenhancement in children and adolescents without a diagnosis of a neurologic disorder is not justifiable. The prescription of neuroenhancements is inadvisable due to numerous social, developmental, and professional integrity issues. Several studies have evaluated atomoxetine for cognitive function in various patient populations, including patients with Huntington disease[12], Alzheimer's disease[13], schizophrenia[14,15], and Parkinson's disease.[16] However, atomoxetine has not demonstrated clinical benefit.

41. **Long-Term Combination Therapy (i.e., > 2 months) with atomoxetine (Strattera, generics) and Central Nervous System (CNS) Stimulants used for the Treatment of Attention Deficit/Hyperactivity Disorder (e.g., mixed amphetamine salts extended-release capsules [Adderall XR®, generics], methylphenidate extended-release tablets, methylphenidate immediate-release tablets).** Currently, data do not support using atomoxetine and CNS stimulant medications concomitantly.[17,18] Short-term drug therapy (2 months or less) with both atomoxetine and CNS stimulant medications are allowed for transitioning the patient to only one drug. Guanfacine extended-release tablets and clonidine extended-release tablets are indicated for use as monotherapy or

as adjunctive therapy to CNS stimulant medications; therefore, long-term combination therapy with either agent and CNS stimulants is appropriate.[2-3]

42. Nocturnal Enuresis. In case reports, children with ADHD and other comorbid psychiatric diagnoses who had nocturnal enuresis and were treated with atomoxetine had resolution of their enuresis.[20] In one controlled trial in pediatric patients (n = 87) with nocturnal enuresis, atomoxetine increased the average number of dry nights per week by 1.47 vs. 0.60 for placebo (P = 0.01).[21] Additional controlled trials with atomoxetine are needed. There are no data with guanfacine extended-release tablets or clonidine extended-release tablets.

43. Weight Loss. In one 12-week, placebo-controlled study in obese women (n = 30), atomoxetine resulted in a mean -3.7% loss vs. 0.2% gain with placebo when combined with a hypocaloric diet (500 kcal/day deficit).[22] Atomoxetine did not demonstrate efficacy for weight reduction in patients with schizophrenia (n = 37) treated with antipsychotics (clozapine or olanzapine).[23] Additional studies are needed.

44. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	No change to criteria.	06/27/2018
Annual revision	In the criteria for Pervasive Developmental Disorders, the "such as" statement was revised from e.g., autism, autistic disorder, Asperger's disorder to e.g., autism spectrum disorder, Asperger's disorder.	07/24/2019
Annual revision	No change to criteria.	08/05/2020

PRIOR AUTHORIZATION POLICY

POLICY: Attention Deficit Hyperactivity Disorder Stimulant Medications Prior Authorization Policy

- Adderall® (dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine sulfate, amphetamine aspartate immediate-release tablets – Teva, generics)
- Adderall XR® (mixed amphetamine salts [dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine sulfate, amphetamine aspartate] extended-release capsules – Shire US, generics)
- Adhansia XR™ (methylphenidate extended-release capsules – Adlon/Purdue)
- Adzenys ER™ (amphetamine extended-release oral suspension – Neos Therapeutics)
- Adzenys XR-ODT™ (amphetamine extended-release orally disintegrating tablets – Neos Therapeutics)
- Aptensio XR™ (methylphenidate extended-release capsules – Rhodes)
- Concerta® (methylphenidate extended-release tablets – Janssen, generics)
- Cotempla XR-ODT™ (methylphenidate extended-release orally disintegrating tablets – Neos Therapeutics)
- Daytrana® (methylphenidate transdermal system – Noven Pharmaceuticals)
- Desoxyn® (methamphetamine tablets – Recordati, generics)
- dextroamphetamine sulfate tablets – generics
- Dexedrine® Spansules® (dextroamphetamine sustained-release capsules – Impax, generics)
- Dyanavel™ XR (amphetamine extended-release oral suspension – Tris)
- Evekeo™ (amphetamine sulfate tablets – Arbor Pharmaceuticals)
- Evekeo ODT™ (amphetamine sulfate orally disintegrating tablets – Arbor Pharmaceuticals)
- Focalin® (dexmethylphenidate immediate-release tablets – Novartis, generics)
- Focalin® XR (dexmethylphenidate extended-release capsules – Novartis, generics)
- Jornay PM™ (methylphenidate hydrochloride extended-release capsules – Ironshore)
- Metadate® CD (methylphenidate extended-release capsules – UCB, generics)
- Metadate® ER (methylphenidate sustained-release tablets – UCB, generics)
- Methylin® (methylphenidate tablets, chewable tablets, and oral solution – Shionogi, generics)
- methylphenidate extended-release capsules (generics to discontinued Methylin™ ER)
- methylphenidate 72 mg extended-release tablets (branded product – Trigen)

- Mydayis™ (mixed salts of a single-entity amphetamine product extended-release capsules – Shire)
- Procentra® (dextroamphetamine sulfate liquid – FSC Laboratories, generics)
- QuilliChew ER™ (methylphenidate extended-release chewable tablets – Pfizer)
- Quillivant™ XR (methylphenidate extended-release oral suspension – Pfizer)
- Relexxii® (methylphenidate extended-release tablets – Vertical [branded generic])
- Ritalin® (methylphenidate immediate-release tablets – Novartis, generics)
- Ritalin® LA (methylphenidate extended-release capsules – Novartis, generics)
- Ritalin SR® (methylphenidate sustained-release tablets – Novartis, generics)
- Vyvanse® (lisdexamfetamine dimesylate capsules and chewable tablets – Shire)
- Zenzedi™ (dextroamphetamine tablets – Arbor Pharmaceuticals)

REVIEW DATE: 08/05/2020

OVERVIEW

The central nervous system (CNS) stimulant medications in this policy are indicated for:[1-24,45,46,50-54]

- **Attention deficit hyperactivity disorder (ADHD)**, treatment. All of the stimulant medications in this policy are indicated for the treatment of ADHD.
- **Binge eating disorder (BED)**, treatment. Vyvanse is the only stimulant medication indicated for the treatment of BED.
- **Narcolepsy**, treatment. Several methylphenidate and amphetamine-containing products are also indicated for the treatment of narcolepsy.
- **Exogenous obesity**, treatment. Evekeo is indicated as adjunctive therapy for the short-term (i.e., a few weeks) treatment of exogenous obesity.

Dextroamphetamine sulfate tablets, Zenzedi, and Adderall (generics) are indicated in patients ≥ 3 years of age; the other products are indicated in patients ≥ 6 years of age, except for Mydayis which is indicated in patients ≥ 13 years of age. Adderall XR (generics), Adzenys ER, Adzenys XR-ODT, Mydayis, Vyvanse, Concerta (generics), and several methylphenidate products are indicated for use in adults with ADHD. Jornay PM is the only stimulant taken in the evening.

Disease Overview

Idiopathic hypersomnia, a condition similar to narcolepsy, is characterized by constant or recurrent daytime sleepiness with no other cause of sleepiness, prolonged nocturnal sleep, difficulty awakening with sleep drunkenness, and long unrefreshing naps with no history of cataplexy.[31-34]

Guidelines

Eating disorders: The American Psychiatric Association (APA) guideline on the treatment of patients with eating disorders (2006 with a Guideline Watch in 2012) suggests treatment with antidepressant medications, particularly selective serotonin reuptake inhibitors (SSRIs), is associated with at least a short-term reduction in binge eating behavior but, in most cases, not with substantial weight loss (recommended with substantial clinical confidence); topiramate is effective for binge reduction and weight loss (recommended with moderate clinical confidence); and zonisamide may produce similar effects regarding weight loss (may be recommended on the basis of individual circumstances).[43,44] The 2012 Guideline Watch references a 2011 literature review by a multinational task force on eating disorders which concluded that Grade A evidence supports the use of imipramine (with moderate risk-benefit ratio), sertraline and citalopram/escitalopram (all with good risk-benefit ratios), and topiramate (with moderate risk-benefit ratio), and Grade D evidence for fluvoxamine and fluoxetine (i.e., inconsistent results).

Narcolepsy and other hypersomnias: The practice parameters from the American Academy of Sleep Medicine for the treatment of narcolepsy and other hypersomnias of central origin, updated in 2007, state that amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of daytime sleepiness due to narcolepsy.[27] The parameters also state that amphetamine, methamphetamine, dextroamphetamine, methylphenidate and modafinil may be effective for the treatment of daytime sleepiness due to idiopathic hypersomnia. As there may be underlying causes/behaviors associated with excessive daytime sleepiness (EDS), a sleep specialist physician has the training to correctly recognize and diagnose this condition.

Major depressive disorder (MDD): The 2010 APA practice guidelines for the treatment of patients with MDD state that many clinicians find augmentation of antidepressants with low doses of stimulants such as methylphenidate or dextroamphetamine may help ameliorate otherwise suboptimally responsive depression, although not all clinical trials have shown benefits from this strategy.[28] There are no clear guidelines regarding the length of time stimulants should be coadministered. A 16-week randomized, double-blind, placebo-controlled trial in patients with geriatric depression in older (mean age of 70 years) outpatients diagnosed with major depression (n = 143) found that combined treatment with citalopram and methylphenidate demonstrated an enhanced clinical response profile in mood and well-being, as well as a higher rate of remission, compared with either drug alone.[47]

Cancer-related fatigue: The National Comprehensive Cancer Network (NCCN) guidelines on cancer-related fatigue (version 2.2020 – May 4, 2020) state to consider use of psychostimulants (i.e., methylphenidate) after other causes of fatigue have been ruled out and/or other management strategies have been attempted.[29] The NCCN guidelines on adult cancer pain (version 1.2020 – April 8, 2020) state that sedation may hinder the achievement of dose titration of opioids to levels that provide adequate analgesia.[30] If opioid-induced sedation develops and persists for greater than 2 to 3 days, it may be managed by administration of a psychostimulant, such as methylphenidate, dextroamphetamine, or modafinil, or by adding caffeine. A meta-analysis of treatments for fatigue associated with palliative care showed a superior effect for methylphenidate in cancer-related fatigue.[48] A review of methylphenidate for cancer-related fatigue found a small but significant improvement in fatigue over placebo (P = 0.005).[49]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of ADHD stimulant medications in adults. Only patients ≥ 18 years of age will be required to meet the Prior Authorization criteria below. All approvals are provided for the duration noted below.

Automation: This policy includes an age edit targeting patients ≥ 18 years of age. Therefore, patients below the age of 18 years will be approved at the point-of-service. For patients ≥ 18 years of age, coverage will be determined by Prior Authorization criteria.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of ADHD stimulant medications is recommended in those who meet the following criteria:

FDA-Approved Indications

8. **Attention Deficit Hyperactivity Disorder.** Approve for 1 year.

2. **Binge Eating Disorder.** Approve only Vyvanse for 1 year if the patient is ≥ 18 years of age.

3. **Narcolepsy.** Approve for 1 year.

Other Uses with Supportive Evidence

4. **Depression, Adjunctive/Augmentation Treatment in Adults.** Approve for 1 year if the patient is concurrently receiving other medication therapy for depression.
   Note: Examples of medications for the treatment of depression include selective serotonin reuptake inhibitors (SSRIs).

5. **Fatigue associated with Cancer and/or its Treatment.** Approve for 1 year.

6. **Idiopathic Hypersomnolence.** Approve for 1 year if the diagnosis is confirmed by a sleep specialist physician or at an institution that specializes in sleep disorders (i.e., sleep center).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of ADHD stimulant medications is not recommended in the following situations:

1. **Fatigue associated with Multiple Sclerosis.** There are no published studies supporting this use. In addition, neither recent review articles nor the 2007 practice parameters for the treatment of narcolepsy and other hypersomnias of central origin mention stimulants (only modafinil). Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin, updated in 2007, state that modafinil may be effective for the treatment of daytime sleepiness due to MS.[27] Agents that have been studied for the treatment of fatigue due to MS include amantadine, modafinil, pemoline, aminopyridines, antidepressants, and aspirin.[41]

45. **Long-term Combination Therapy (i.e., > 2 months) with Strattera® (atomoxetine capsules) and Central Nervous System (CNS) Stimulants for the treatment of Attention Deficit/Hyperactivity Disorder (e.g., mixed amphetamine salts extended-release capsules [Adderall XR®, generics], methylphenidate extended-release tablets, methylphenidate immediate-release tablets).** Currently, data do not support using Strattera and CNS stimulant medications concomitantly.[42] Short-term drug therapy (≤ 2 months) with both Strattera and CNS stimulant medications are allowed for transitioning the patient to only one drug. Intuniv and clonidine extended-release tablets (Kapvay, generics) are indicated for use as monotherapy, or as adjunctive therapy to CNS stimulant medications; therefore, long-term combination therapy with either agent and CNS stimulants is appropriate.[35-36]

46. **Neuroenhancement.** The use of prescription medication to augment cognitive or affective function in otherwise healthy individuals (also known as neuroenhancement) is increasing in adult and pediatric populations.[37] A 2013 Ethics, Law, and Humanities Committee position paper, endorsed by the American Academy of Neurology (AAN) indicates that based on available data and the balance of ethics issues, neuroenhancement in legally and developmentally nonautonomous children and adolescents without a diagnosis of a neurologic disorder is not justifiable. In nearly autonomous adolescents, the fiduciary obligation of the physician may be weaker, but the prescription of neuroenhancements is inadvisable due to numerous social, developmental, and professional integrity issues.

47. **Weight Loss.** Of the CNS stimulants, only amphetamine and methamphetamine are indicated for exogenous obesity, as a short-term (i.e., a few weeks) adjunct in a regimen of weight reduction based on caloric restriction, for patients in whom obesity is refractory to alternative therapy (e.g., repeated diets, group programs, and other drugs).[4,41] However, guidelines on the management of obesity do not address or recommend use of amphetamine or methamphetamine (or any other CNS stimulants).[38-40]

48. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Update	2/7/2018: Addition of methylphenidate 72 mg extended-release tablets (branded product) to the policy.	--
Update	3/28/2018: Addition of Adzenys ER to the policy.	--
Annual revision	No change to criteria.	10/3/2018
Selected revision	Addition of Jornay PM to the policy. No change to criteria.	06/18/2019
Annual revision	Addition of Adhansia XR and Evekeo ODT to the policy. For the approval condition of Binge Eating Disorder, the requirement to have tried one medication for binge eating disorder prior to Vyvanse approval was removed.	08/07/2019
Annual revision	No change to criteria.	08/05/2020
Update	10/28/2020: Addition of Relexxii to the policy.	--

PRIOR AUTHORIZATION POLICY

POLICY: Bone Modifiers – Evenity Prior Authorization Policy

- Evenity® (romosozumab-aqqg injection for subcutaneous use – Amgen)

REVIEW DATE: 04/22/2020

OVERVIEW

Evenity, a sclerostin inhibitor, is indicated for the treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.[1] According to the Evenity prescribing information, the anabolic effect of Evenity wanes after 12 monthly doses of therapy. Therefore, limit the duration of use to 12 monthly doses. If osteoporosis therapy remains warranted, continued therapy with an anti-resorptive therapy (e.g., alendronate) should be considered.

Guidelines

Many guidelines are available regarding the management of postmenopausal osteoporosis.[2-5] In general, the guidelines recommend bisphosphonate therapy as initially for women in whom pharmacologic therapy is warranted (e.g., women at high risk of fractures) to reduce the risk of fractures. For patients who are extremely high risk of fracture (e.g., previously experienced an osteoporotic or fragility fracture) other osteoporosis therapies are recommended. Other agents are also recommended for women who cannot take bisphosphonate therapy (e.g., patients with severe renal impairment [creatinine clearance < 35 mL/min], chronic kidney disease) or who have an underlying gastrointestinal condition (e.g., esophageal lesions). In general, osteoporosis is defined by the presence of fragility fractures or among women with a T-score of -2.5 or lower in the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius.[2] Therapy is also recommended among women who have a T-score between -1.0 and -2.5 if a substantial risk for major osteoporotic fracture is present (e.g., Fracture Risk Assessment Tool [FRAX®] score suggests high risk).

In 2020 the Endocrine Society issued a guideline update regarding the pharmacological management of osteoporosis in postmenopausal women which addressed Evenity.[6] In postmenopausal women with osteoporosis at very high risk of fractures such as patients with severe osteoporosis (i.e., low T-score < -2.5 and fractures) or multiple fractures, Evenity therapy is recommended for up to 1 year for the reduction of vertebral, hip, and nonvertebral fractures. The recommended dose is 210 mg monthly by SC injection for 12 months. In postmenopausal women with osteoporosis who have completed a course of Evenity, antiresorptive osteoporosis therapy is recommended to maintain bone density gains and reduce fracture risk.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Evenity. Coverage is limited to 12 monthly doses during the therapy course.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Evenity is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Osteoporosis Treatment for a Postmenopausal Patient.** Approve for 1 year if the patient meets the following criteria (A, B and C):
   - **A)** The patient meets ONE of the following conditions (i, ii, or iii):
     - **i.** The patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip and/or 33% (one-third) radius (wrist); OR
     - **ii.** The patient has had an osteoporotic fracture or a fragility fracture; OR

iii. The patient has low bone mass (T-score [current or at any time in the past] between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% [one third] radius [wrist]) and the physician determines that the patient it at high risk for fracture; AND

B) The patient meets ONE of the following (i, ii, iii, or iv):

i. The patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a, b, or c):

a) The patient has had an inadequate response to oral bisphosphonate therapy after a trial duration of 12 months as determined by the prescribing physician (e.g., ongoing and significant loss of bone mineral density (BMD), lack of BMD increase); OR

b) The patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy; OR

c) The patient has experienced intolerability to an oral bisphosphonate (e.g., severe gastrointestinal [GI]-related adverse events, severe musculoskeletal-related adverse events, a femoral fracture); OR

ii. The patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):

a) The patient cannot swallow or has difficulty swallowing; OR

b) The patient cannot remain in an upright position post oral bisphosphonate administration; OR

c) The patient has a pre-existing gastrointestinal (GI) medical condition (e.g., patient with esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying [stricture, achalasia]); OR

iii. The patient has tried ibandronate injection (Boniva IV) or zoledronic acid injection (Reclast); OR

iv. The patient meets one of the following conditions (a, b or c):

a) Severe renal impairment (creatinine clearance < 35 mL/min); OR

b) Chronic kidney disease; OR

c) The patient has had an osteoporotic fracture or a fragility fracture; AND

C) The patient has received no more than 12 monthly doses during this therapy course.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Evenity is not recommended in the following situations:

49. Osteoporosis Prevention. Evenity is not indicated for the prevention of osteoporosis. **Concurrent Use with Other Medications for Osteoporosis.**
Note: Examples include oral bisphosphonates (e.g., alendronate, risedronate, ibandronate), intravenous bisphosphonates (zoledronic acid injection [Reclast], intravenous ibandronate), Prolia® (denosumab injection for subcutaneous use), teriparatide injection for subcutaneous use (Forteo®/Bonsity®), Tymlos® (abaloparatide injection for subcutaneous use), and calcitonin nasal spray (Miacalcin®/Fortical®).

50. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	04/10/2019
Selected Revision	**Osteoporosis Treatment for a Postmenopausal Patient:** The criterion that requires that the patient has received no more than 12 monthly doses during their lifetime was modified to remove "their lifetime" and replaced with the phrasing "this therapy course."	05/08/2019
Annual Revision	The following changes were made: 1. **Conditions Not Recommended for Approval:** For the criteria regarding Concurrent Use of Other Medications for Osteoporosis, the examples of other medications used for osteoporosis were moved from the criteria to a note. Reference to calcium and vitamin D was deleted.	04/22/2020

PRIOR AUTHORIZATION POLICY

POLICY: Bone Modifiers – Ibandronate Intravenous (Boniva IV) Prior Authorization Policy
- Boniva® (ibandronate injection – Genentech/Roche, generics)

REVIEW DATE: 03/03/2021

OVERVIEW
Ibandronate injection (Boniva IV) is indicated for the treatment of osteoporosis in postmenopausal women.[1]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of ibandronate injection (Boniva IV). All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of ibandronate injection (Boniva IV) is recommended in those who meet the following criteria:

FDA-Approved Indication

2. Osteoporosis – Treatment for a Postmenopausal Patient. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient meets ONE of the following conditions (i, ii, or iii):
  - **iv.** Patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip and/or 33% (one-third) radius (wrist); OR

v. Patient has had an osteoporotic fracture or a fragility fracture; OR

vi. Patient meets both of the following (a and b):

a) Patient has low bone mass; AND

Note: An example of low bone mass includes a T-score (current or at any time in the past) between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip and/or 33% (one-third) radius (wrist).

b) According to the prescriber, patient is at high risk for fracture; AND

B) Patient meets ONE of the following (i, ii, iii, or iv):

i. Patient has tried ibandronate injection (Boniva) or zoledronic acid injection (Reclast); OR

ii. Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a, b, or c):

Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).

a) According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR

Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD) and lack of a BMD increase.

b) Patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy; OR

c) Patient has experienced significant intolerance to an oral bisphosphonate; OR

Note: Examples of significant intolerance include severe gastrointestinal related adverse events, severe musculoskeletal related adverse events, or a femoral fracture.

iii. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):

a) Patient cannot swallow or has difficulty swallowing; OR

b) Patient cannot remain in an upright position post oral bisphosphonate administration; OR

c) Patient has a pre-existing gastrointestinal medical condition in which intravenous bisphosphonate therapy may be warranted; OR

Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).

iv. Patient has had an osteoporotic fracture or a fragility fracture.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of ibandronate injection (Boniva IV) is not recommended in the following situations:

51. Osteoporosis Prevention. Ibandronate injection (Boniva IV) is not indicated for the prevention of osteoporosis and supporting data are limited.

52. Concurrent Use of Ibandronate Injection (Boniva IV) with Other Medications for Osteoporosis.

Note: Examples of other medications for osteoporosis include oral bisphosphonates (e.g., alendronate, risedronate, ibandronate), other intravenous bisphosphonates (e.g., zoledronic acid injection [Reclast]), Prolia (denosumab injection for subcutaneous use), Evenity (romosozumab-aqqg injection for subcutaneous use), Forteo (teriparatide injection for subcutaneous use, generic), Tymlos (abaloparatide injection for subcutaneous use), and calcitonin nasal spray.

53. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Boniva® injection for intravenous use [prescribing information]. South San Francisco, CA: Genentech USA/Roche; April 2019.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Previously, the policy was entitled "Bone Modifiers – Bisphosphonates (intravenous)" and included Boniva IV and Reclast. These policies were divided such that this policy only includes Boniva IV and is titled "Bone Modifiers – Ibandronate IV (Boniva IV). Approval durations changed from 3 years to 1 year for osteoporosis treatment for a postmenopausal patient.	02/27/2019
Annual Revision	In the Conditions Not Recommended for Approval section, added medication examples that ibandronate IV should not be used with concomitantly (e.g., Bonsity, Evenity, and provided examples of bisphosphonates).	02/26/2020
Annual Revision	1. **Osteoporosis – Treatment for a Postmenopausal Patient.** The criteria that requires low bone mass had the definition moved from the criteria to a Note and the wording was changed from "prescribing physician" to "prescriber". For the criteria requiring a trial of one oral bisphosphonate, the criteria were changed to state "at least one" and examples of oral bisphosphonates were added to a Note. Wording for the criterion regarding inadequate response to an oral bisphosphonate was changed to "experienced inadequate efficacy" and "prescribing physician" was changed to "prescriber". Examples of inadequate efficacy to an oral bisphosphonate were moved from the criteria to a Note. Wording of the criterion regarding intolerability to an oral bisphosphonate was changed to "experienced significant intolerance". Examples of significant intolerance were moved from the criteria to a Note. For the criterion that addresses if the patient has a pre-existing gastrointestinal medical condition, examples were moved from the criteria to a Note. 2. **Conditions Not Recommended for Approval:** For the notation cited regarding "Concurrent Use of Ibrandronate Injection (Boniva Intravenous) with Other Medications for Osteoporosis" the examples of medications were moved from the criteria to a Note; the medication list was revised. Also, the wording stating "except calcium and vitamin D" was removed.	03/03/2021

PRIOR AUTHORIZATION POLICY

POLICY: Bone Modifiers – Prolia Prior Authorization Policy

- Prolia® (denosumab injection for subcutaneous use – Amgen)

REVIEW DATE: 07/29/2020

OVERVIEW

Prolia, a receptor activator of nuclear factor kappa-B (RANK) ligand inhibitor, is indicated for the following uses:[1]

- **Bone loss (treatment to increase bone mass), in men with nonmetastatic prostate cancer** at high risk for fracture receiving androgen deprivation therapy (ADT).
- **Bone loss (treatment to increase bone mass), in women with breast cancer** at high risk for fracture receiving adjuvant aromatase inhibitor (AI) therapy.
- **Glucocorticoid-induced osteoporosis** (treatment), in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months.
- **Osteoporosis,** treatment of **postmenopausal women** at high risk of fracture.
- **Osteoporosis,** treatment to **increase bone mass in men** at high risk for fracture.

In general, high risk of fractures is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.[1] Of note, denosumab subcutaneous injection is also available under the brand name Xgeva®, and is indicated for the prevention of skeletal-related events in patients with multiple myeloma, as well as in patients with bone metastases from solid tumors, giant cell tumor of bone, and hypercalcemia of malignancy.[2]

Dosing Information

For all indications, the dose is 60 mg once every 6 months as a subcutaneous injection.[1]

Guidelines

Several guidelines address Prolia.

- **Breast Cancer/Prostate Cancer:** The National Comprehensive Cancer Network (NCCN) guidelines for breast cancer (version 5.2020 – July 15, 2020)[6] and prostate cancer (version 2.2020 – May 21, 2020)[7] note that if patients are receiving agents that impact bone mineral density (BMD), bisphosphonates (oral/intravenous), as well as Prolia, should be considered to maintain or improve BMD and/or reduce the risk of fractures.
- **Glucocorticoid-Induced Osteoporosis (GIO):** In 2017, the American College of Rheumatology (ACR) updated guidelines for the prevention and treatment of GIO.[5] In various clinical scenarios, oral bisphosphonates are preferred, followed by intravenous bisphosphonates (e.g., zoledronic acid injection).
- **Postmenopausal Osteoporosis:** Prolia is prominently featured in guidelines for postmenopausal osteoporosis by the Endocrine Society (2019)[3] and the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) [2020][4]. Prolia is one of among several agents cited as an alternative for patients at high risk for fractures.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Prolia. All approvals are provided for 1 year in duration. In the approval indication, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

Automation: Smart Coverage Review uses patient claim history to answer Prior Authorization questions regarding medication history of Boniva® (ibandronate injection for intravenous use) or Reclast® (zoledronic acid injection for intravenous use). A 2-year look back period will be used to check claim history and automate for use of either agent (Boniva intravenous or Reclast). If not in claims, medication history can be obtained through Prior Authorization criteria. For all reviews, other Prior Authorization criteria listed below will also be applied.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Prolia is recommended in those who meet the following criteria:

FDA-Approved Indications

17. **Bone Loss (Treatment to Increase Bone Mass) in Patients with Breast Cancer at High Risk for Fracture Receiving Adjuvant Aromatase Inhibitor Therapy.** Approve for 1 year if the patient meets the following criteria (A and B):
    - **A)** Patient has breast cancer that is not metastatic to bone; AND
    - **B)** Patient is receiving aromatase inhibitor therapy (e.g., anastrozole, letrozole, or exemestane).

18. **Bone Loss (Treatment to Increase Bone Mass) in Patients with Nonmetastatic Prostate Cancer at High Risk for Fracture Receiving Androgen Deprivation Therapy.** Approve for 1 year if the patient meets the following criteria (A and B):
    - **A)** Patient has prostate cancer that is not metastatic to bone; AND
    - **B)** Patient meets ONE of the following conditions (i or ii):
        - **i.** Patient is receiving androgen deprivation therapy (e.g., Lupron Depot® [leuprolide for depot suspension], Eligard® [leuprolide acetate for injectable suspension], Trelstar® [triptorelin pamoate for injectable suspension], or Zoladex® [goserelin implant]); OR
        - **ii.** Patient has undergone bilateral orchiectomy.

19. **Glucocorticoid-Induced Osteoporosis – Treatment.** Approve for 1 year if the patient meets the following criteria (A and B):
    - **A)** Patient is either initiating or continuing systemic glucocorticoids (e.g., prednisone); AND
    - **B)** Patient meets ONE of the following (i, ii, iii, or iv):
        - **i.** Patient has tried zoledronic acid injection (Reclast); OR
        - **ii.** Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a, b, or c):
          Note: Examples of oral bisphosphonate products include Fosamax® (alendronate tablets and oral solution), Fosamax® Plus D (alendronate/cholecalciferol tablets), Actonel® (risedronate tablets), Atelvia® (risedronate delayed-release tablets), and Boniva® (ibandronate tablets).
            - **a)** Patient has had an inadequate response to oral bisphosphonate therapy after a trial duration of 12 months as determined by the prescriber (e.g., ongoing and significant loss of bone mineral density [BMD], lack of BMD increase); OR
            - **b)** Patient has had an osteoporotic fracture or fragility fracture while receiving oral bisphosphonate therapy; OR

c) Patient has experienced intolerability to an oral bisphosphonate (e.g., severe gastrointestinal [GI]-related adverse effects, severe musculoskeletal-related side effects, a femoral fracture); OR

iii. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):
- **a)** Patient cannot swallow or has difficulty swallowing; OR
- **b)** Patient cannot remain in an upright position post oral bisphosphonate administration; OR
- **c)** Patient has a pre-existing gastrointestinal (GI) medical condition (e.g., patient with esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying [stricture, achalasia]); OR

iv. Patient meets one of the following conditions (a, b, or c):
- **a)** Severe renal impairment (creatinine clearance < 35 mL/min); OR
- **b)** Chronic kidney disease (CKD); OR
- **c)** Patient has had an osteoporotic fracture or a fragility fracture.

~~**20.**~~ **Osteoporosis Treatment for a Postmenopausal Patient.** Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient meets ONE of the following conditions (i, ii, or iii):
- **i.** Patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius (wrist); OR
- **ii.** Patient has had an osteoporotic fracture or a fragility fracture; OR
- **iii.** Patient meets both of the following (a and b):
  - **a)** Patient has low bone mass (T-score [current or at any time in the past] between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip and/or 33% [one-third] radius [wrist]); AND
  - **b)** Prescriber determines the patient is at high risk for fracture; AND

B) Patient meets ONE of the following (i, ii, iii, or iv):
- **i.** Patient has tried ibandronate injection (Boniva) or zoledronic acid injection (Reclast); OR
- **ii.** Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a, b, or c):

  Note: Examples of oral bisphosphonate products include Fosamax® (alendronate tablets and oral solution), Fosamax® Plus D (alendronate/cholecalciferol tablets), Actonel® (risedronate tablets), Atelvia® (risedronate delayed-release tablets), and Boniva® (ibandronate tablets).
  - **a)** Patient has had an inadequate response to oral bisphosphonate therapy after a trial duration of 12 months as determined by the prescriber (e.g., ongoing and significant loss of bone mineral density (BMD), lack of BMD increase); OR
  - **b)** Patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy; OR
  - **c)** Patient has experienced intolerability to an oral bisphosphonate (e.g., severe gastrointestinal-related adverse effects, severe musculoskeletal-related side effects, a femoral fracture); OR
- **iii.** Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):
  - **a)** Patient cannot swallow or has difficulty swallowing; OR
  - **b)** Patient cannot remain in an upright position post oral bisphosphonate administration; OR
  - **c)** Patient has a pre-existing gastrointestinal medical condition (e.g., patient with esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying [stricture, achalasia]); OR
- **iv.** Patient meets one of the following conditions (a, b, or c):
  - **a)** Severe renal impairment (creatinine clearance < 35 mL/min); OR
  - **b)** Chronic kidney disease (CKD); OR

c) Patient has had an osteoporotic fracture or a fragility fracture.

21. Osteoporosis – Treatment (to Increase Bone Mass) for Men*. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient meets ONE of the following conditions (i, ii, or iii):

i. Patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip and/or 33% (one-third) radius (wrist); OR

ii. Patient has had an osteoporotic fracture or a fragility fracture; OR

iii. Patient meets both of the following (a and b):

a) Patient has low bone mass (T-score [current or at any time in the past] between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip and/or 33% [one-third] radius [wrist]); AND

b) Prescriber determines the patient is at high risk of fracture; AND

B) Patient meets ONE of the following (i, ii, iii or iv):

i. Patient has tried zoledronic acid injection (Reclast); OR

ii. Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a, b, or c):

Note: Examples of oral bisphosphonate products include Fosamax® (alendronate tablets and oral solution), Fosamax® Plus D (alendronate/cholecalciferol tablets), Actonel® (risedronate tablets), Atelvia® (risedronate delayed-release tablets), and Boniva® (ibandronate tablets).

a) Patient has had an inadequate response to oral bisphosphonate therapy after a trial duration of 12 months as determined by the prescriber (e.g., ongoing and significant loss of bone marrow density [BMD], lack of BMD increase); OR

b) Patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy; OR

c) Patient has experienced intolerability to an oral bisphosphonate (e.g., severe gastrointestinal [GI]-related adverse effects, severe musculoskeletal-related side effects, a femoral fracture); OR

iii. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b or c):

a) Patient cannot swallow or has difficulty swallowing; OR

b) Patient cannot remain in an upright position post oral bisphosphonate administration; OR

c) Patient has a pre-existing GI medical condition (e.g., patient with esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying [stricture, achalasia]); OR

iv. Patient meets one of the following conditions (a, b, or c):

a) Severe renal impairment (creatinine clearance < 35 mL/min); OR

b) Chronic kidney disease (CKD); OR

c) Patient has had an osteoporotic fracture or a fragility fracture.

* Refer to the Policy Statement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Prolia is not recommended in the following situations:

54. Concurrent Use with Other Medications for Osteoporosis.

Note: Examples include teriparatide injection for subcutaneous use (Forteo®/Bonsity®), Tymlos® (abaloparatide injection for subcutaneous use), oral bisphosphonates (e.g., alendronate, risedronate, ibandronate), intravenous bisphosphonates (zoledronic acid injection [Reclast], intravenous

ibandronate), calcitonin nasal spray (Miacalcin®/Fortical®), and Evenity® (romosozumab-aqqg injection for subcutaneous use). Prolia is not indicated for use as combination therapy.[1]

55. **Giant Cell Tumor of Bone.** Studies with denosumab in giant cell tumor of the bone used dosing for Xgeva, which is indicated for the treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.[2]
56. **Osteoporosis Prevention.** Prolia is not indicated for the prevention of osteoporosis.[1]

57. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	Criteria added regarding GIO treatment.	06/20/2018
Annual revision	Approval durations for all FDA-approved uses were changed from 3 years to 1 year. The following criteria changes were made: **Conditions Not Recommended for Approval:** Added Evenity to the list of medications that should not be used concomitantly with Prolia.	07/03/2019
Annual revision	In related criteria the word "prescriber" is replacing the word/phrase "physician" or "prescribing physician". Additionally, the following changes were made: **Automation:** Automation was previously listed as "None". Smart Coverage Review automation was added. **Conditions Not Recommended for Approval:** For the criteria regarding Concurrent Use of Other Medications for Osteoporosis, the examples of other medications used for osteoporosis in the note were revised. Reference to calcium and vitamin D was deleted.	07/29/2020
Update	08/29/2020: No criteria changes: For the conditions that require a trial of at least one oral bisphosphonate or an oral bisphosphonate-containing product (glucocorticoid-induced osteoporosis – treatment; osteoporosis treatment for a postmenopausal patient, and osteoporosis treatment [to increase bone mass] for men), added a note that provided examples of these products (Note: Examples of oral bisphosphonate products include Fosamax® [alendronate tablets and oral solution], Fosamax® Plus D [alendronate/cholecalciferol tablets], Actonel® [risedronate tablets], Atelvia® [risedronate delayed-release tablets], and Boniva® [ibandronate tablets]).	--

PRIOR AUTHORIZATION POLICY

POLICY: Bone Modifiers – Teriparatide Products Prior Authorization Policy

- Forteo® (teriparatide injection for subcutaneous injection – Eli Lilly)
- Teriparatide injection for subcutaneous use – Alvogen

REVIEW DATE: 07/29/2020; selected revision 02/24/2021

OVERVIEW

Teriparatide products, recombinant human parathyroid hormone (PTH) [1-34], are indicated for the following uses:[1-3]

- **Glucocorticoid-induced osteoporosis (treatment)**, in men and women at high risk for fracture associated with sustained systemic glucocorticoid therapy (daily dosage equivalent to 5 mg or greater of prednisone).
- **Osteoporosis, treatment of postmenopausal women** at high risk for fracture.
- **Osteoporosis, to increase bone mass in men with primary or hypogonadal osteoporosis** at high risk for fracture.

In general, for all indications, patients at high risk for fracture are defined as those with a history of osteoporotic fractures, have multiple risk factors for fracture, or have failed or are intolerant to other osteoporosis therapy.[1-3]

Teriparatide has been used for patients with hypoparathyroidism.[4-11] Natpara® (parathyroid hormone injection for subcutaneous use) is indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism.[12] However, there is a recall of Natpara and teriparatide is one of two main alternatives recommended in a joint guidance statement from the American Society for Bone and Mineral Research and Endocrine Society for patients with hypoparathyroidism transitioning from

Natpara.[13] It is notable that if teriparatide therapy is used in this clinical scenario, twice daily or even three times daily injections are usually needed.

Guidelines

Teriparatide is addressed in various clinical guidelines.[14-16]

- **Glucocorticoid-Induced Osteoporosis (GIO):** The American College of Rheumatology updated guidelines for the prevention and treatment of GIO (2017).[16] In various clinical scenarios, teriparatide is recommended after trial of other agents (e.g., oral bisphosphonates, intravenous bisphosphonates).
- **Postmenopausal Osteoporosis:** Teriparatide products are mentioned in guidelines for postmenopausal osteoporosis by the Endocrine Society (2019)[14] and the American Association of Clinical Endocrinologists and the American College of Endocrinology (2020)[15]. Teriparatide is one of among several agents cited as an alternative for patients at very high risk for fractures or among those who cannot tolerate oral therapy.

Safety

An increased incidence of osteosarcoma was noted in male and females rates who received teriparatide.[1] Osteosarcoma has been reported in patients treated with teriparatide in the postmarketing setting, however, an increased risk of osteosarcoma has not been observed in observational studies involving humans. There are limited data evaluating the risk of osteosarcoma beyond 2 years of teriparatide use. Avoid use of teriparatide in patients with a baseline risk of osteosarcoma.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of teriparatide products. All approval(s) are provided for 2 years in duration unless otherwise noted below. For the indication of hypoparathyroidism, because of the specialized skills required for evaluation and diagnosis of patients treated with teriparatide as well as monitoring for adverse events and long-term efficacy, approval requires teriparatide to be prescribed by or in consultation with a physician who specialized in the condition being treated. In the approval indication, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

Automation: Smart Coverage Review uses patient claim history to answer Prior Authorization questions regarding medication history of Boniva® (ibandronate injection for intravenous use) or Reclast® (zoledronic acid injection for intravenous use). A 2-year look back period will be used to check claim history and automate for use of either agent (Boniva intravenous or Reclast). If not in claims, medication history can be obtained through Prior Authorization criteria. For all reviews, other Prior Authorization criteria listed below will also be applied.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of teriparatide products is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Glucocorticoid-Induced Osteoporosis – Treatment.** Approve for 2 years if the patient meets the following criteria (A, B, and C):
   - **C)** Patient is either initiating or continuing systemic glucocorticoids; AND
     Note: An example of a systemic glucocorticoid is prednisone.
   - **D)** Patient meets ONE of the following (i, ii, iii, or iv):

v. Patient has tried zoledronic acid injection (Reclast); OR

vi. Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a, b, or c):

Note: Examples of oral bisphosphonate products include Fosamax® (alendronate tablets and oral solution), Fosamax® Plus D (alendronate/cholecalciferol tablets), Actonel® (risedronate tablets), Atelvia® (risedronate delayed-release tablets), and Boniva® (ibandronate tablets).

d) Patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months as determined by the prescriber; OR

Note: An example of an inadequate efficacy is ongoing and significant loss of bone mineral density (BMD) or a lack of a BMD increase.

e) Patient has had an osteoporotic fracture or fragility fracture while receiving oral bisphosphonate therapy; OR

f) Patient has experienced significant intolerance to an oral bisphosphonate; OR

Note: Examples of significant intolerance include severe gastrointestinal related adverse events, severe musculoskeletal related adverse events, or a femoral fracture.

vii. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):

d) Patient cannot swallow or has difficulty swallowing; OR

e) Patient cannot remain in an upright position post oral bisphosphonate administration; OR

f) Patient has a pre-existing gastrointestinal (GI) medical condition; OR

Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).

viii. Patient meets one of the following conditions (a, b, or c):

d) Severe renal impairment; OR

Note: An example of severe renal impairment is a creatinine clearance < 35 mL/min.

e) Chronic kidney disease (CKD); OR

f) Patient has had an osteoporotic fracture or a fragility fracture; AND

E) Use of teriparatide exceeding 2 years during a patient's lifetime, approve if the patient is at high risk for fracture as determined by the prescriber.

Note: Examples of high risk for fracture include a previous osteoporotic fracture or fragility fracture, receipt of medications that increase the risk of osteoporosis, advanced age, and very low bone mineral density.

2. Osteoporosis – Treatment for a Postmenopausal Patient. Approve for 2 years if the patient meets the following criteria (A, B, and C):

A) Patient meets ONE of the following conditions (i, ii, or iii):

i. Patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius (wrist); OR

ii. Patient has had an osteoporotic fracture or a fragility fracture; OR

iii. Patient meets both of the following (a and b):

a) Patient has low bone mass; AND

Note: An example of low bone mass includes a T-score (current or at any time in the past) between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip and/or 33% (one-third) radius (wrist).

b) Prescriber determines the patient is at high risk for fracture; AND

B) Patient meets ONE of the following (i, ii, iii, or iv):

ii. Patient has tried ibandronate injection (Boniva) or zoledronic acid injection (Reclast); OR

iii. Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a, b, or c):
Note: Examples of oral bisphosphonate products include Fosamax® (alendronate tablets and oral solution), Fosamax® Plus D (alendronate/cholecalciferol tablets), Actonel® (risedronate tablets), Atelvia® (risedronate delayed-release tablets), and Boniva® (ibandronate tablets).
a) Patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months as determined by the prescriber; OR
Note: An example of an inadequate efficacy is ongoing and significant loss of bone mineral density (BMD) or a lack of a BMD increase.
b) Patient has had an osteoporotic fracture or fragility fracture while receiving oral bisphosphonate therapy; OR
c) Patient has experienced significant intolerance to an oral bisphosphonate; OR
Note: Examples of significant intolerance include severe gastrointestinal related adverse events, severe musculoskeletal related adverse events, or a femoral fracture.

iv. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):
a) Patient cannot swallow or has difficulty swallowing; OR
b) Patient cannot remain in an upright position post oral bisphosphonate administration; OR
c) Patient has a pre-existing gastrointestinal (GI) medical condition; OR
Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).

v. Patient meets one of the following conditions (a, b, or c):
a) Severe renal impairment; OR
Note: An example of severe renal impairment is a creatinine clearance < 35 mL/min.
b) Chronic kidney disease (CKD); OR
c) Patient has had an osteoporotic fracture or a fragility fracture; AND

C) Use of teriparatide exceeding 2 years during a patient's lifetime, approve if the patient is at high risk for fracture as determined by the prescriber.
Note: Examples of high risk for fracture include a previous osteoporotic fracture or fragility fracture, receipt of medications that increase the risk of osteoporosis, advanced age, and very low bone mineral density.

3. Osteoporosis – (to Increase Bone Mass) in Men* with Primary or Hypogonadal Osteoporosis. Approve for 2 years if the patient meets the following criteria (A, B and C):

A) Patient meets ONE of the following conditions (i, ii, or iii):
i. Patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip and/or 33% (one-third) radius (wrist); OR
ii. Patient has had an osteoporotic fracture or a fragility fracture; OR
iii. Patient meets both of the following (a and b):
a) Patient has low bone mass; AND
Note: An example of low bone mass includes a T-score (current or at any time in the past) between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip and/or 33% (one-third) radius (wrist).
b) Prescriber determines the patient is at high risk for fracture; AND

B) Patient meets one of the following (i, ii, iii, or iv):
i. Patient has tried zoledronic acid injection (Reclast); OR
ii. Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a, b, or c):

Note: Examples of oral bisphosphonate products include Fosamax® (alendronate tablets and oral solution), Fosamax® Plus D (alendronate/cholecalciferol tablets), Actonel® (risedronate tablets), Atelvia® (risedronate delayed-release tablets), and Boniva® (ibandronate tablets).

a) Patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months as determined by the prescriber; OR
Note: An example of an inadequate efficacy is ongoing and significant loss of bone mineral density (BMD) or a lack of a BMD increase.

b) Patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy; OR

c) Patient has experienced significant intolerance to an oral bisphosphonate; OR
Note: Examples of significant intolerance include severe gastrointestinal related adverse events, severe musculoskeletal related adverse events, or a femoral fracture.

iii. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):

a) Patient cannot swallow or has difficulty swallowing; OR

b) Patient cannot remain in an upright position post oral bisphosphonate administration; OR

c) Patient has a pre-existing gastrointestinal medical condition; OR
Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying (e.g., stricture, achalasia).

iv. Patient meets one of the following conditions (a, b, or c):

a) Severe renal impairment; OR
Note: An example of severe renal impairment is a creatinine clearance < 35 mL/min.

b) Chronic kidney disease (CKD); OR

c) Patient has had an osteoporotic fracture or a fragility fracture; AND

C) Use of teriparatide exceeding 2 years during a patient's lifetime, approve if the patient is at high risk for fracture as determined by the prescriber.
Note: Examples of high risk for fracture include a previous osteoporotic fracture or fragility fracture, receipt of medications that increase the risk of osteoporosis, advanced age, and very low bone mineral density.

***** Refer to the Policy Statement.

Other Uses with Supportive Evidence

4. Hypoparathyroidism. Approve for 2 years if the patient meets the following criteria (A and B):

1. Patient meets one of the following (i or ii):
   i. Patient has tried Natpara (parathyroid hormone injection); OR
   ii. Natpara is not available; AND
   Note: Approval for this use is a unique circumstance and the other criterion regarding the other indications do not apply.
2. Medication is prescribed by or in consultation with an endocrinologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of teriparatide is not recommended in the following situations:

58. Concurrent Use with Other Medications for Osteoporosis.

Note: Examples include Prolia® (denosumab injection for subcutaneous use), oral bisphosphonates (e.g., alendronate, risedronate, ibandronate), intravenous bisphosphonates (zoledronic acid injection [Reclast], intravenous ibandronate), calcitonin nasal spray (Miacalcin®/Fortical®), Tymlos® (abaloparatide injection for subcutaneous use) and Evenity® (romosozumab-aqqg injection for subcutaneous use).

59. Osteoporosis Prevention. Teriparatide products have not been studied in this patient population. The benefits and risks of building bone with teriparatide products in a condition in which substantial bone loss has not occurred have not been investigated.[1]

60. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated, as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	In related criteria the word "prescriber" is replacing the word/phrase "physician" or "prescribing physician". An authorized generic to Bonsity (teriparatide) was added to the Policy. The same criteria as that in place for Forteo and Bonsity apply. Additionally, the following changes were made: **Automation:** Automation was previously listed as "None". Smart Coverage Review automation was added.	07/29/2020

	Other Uses with Supportive Evidence: For the criteria regarding Concurrent Use of Other Medications for Osteoporosis, the examples of other medications used for osteoporosis in the note were revised. Reference to calcium and vitamin D was deleted.	
Update	08/29/2020: No criteria changes: For the conditions that require a trial of at least one oral bisphosphonate or an oral bisphosphonate-containing product (glucocorticoid-induced osteoporosis – treatment; osteoporosis treatment for a postmenopausal patient, and osteoporosis treatment [to increase bone mass] for men), added a note that provided examples of these products (Note: Examples of oral bisphosphonate products include Fosamax® [alendronate tablets and oral solution], Fosamax® Plus D [alendronate/cholecalciferol tablets], Actonel® [risedronate tablets], Atelvia® [risedronate delayed-release tablets], and Boniva® [ibandronate tablets]).	--

HISTORY (continued)

Type of Revision	Summary of Changes	Review Date
Selected Revision	Bonsity was removed from the listing of products as it was launched in the US as Teriparatide manufactured by Alvogen. The following sentence in the Policy Statement was removed: "Coverage cumulative with teriparatide product and Tymlos is recommended for up to 2 years of a patient's lifetime". The following criteria changes were made: **Glucocorticoid-Induced Osteoporosis – Treatment:** Regarding the approval duration, wording was changed from "Approve for up to 2 years (total)" to "approve for 2 years". The criteria which stated that "Use of teriparatide and/or Tymlos does not exceed 2 years during a patient's lifetime" was changed to "approve use of teriparatide exceeding 2 years during a patient's lifetime if the patient is at high risk for fracture as determined by the prescriber." Examples of high fracture risk are provided in a Note. The example of prednisone as a systemic glucocorticoid was moved from the criteria to a Note. Wording for the criterion regarding inadequate response to an oral bisphosphonate was changed to "experienced inadequate efficacy". Examples of inadequate efficacy to an oral bisphosphonate were moved from the criteria to a Note. Wording of the criterion regarding intolerability to an oral bisphosphonate was changed to "experienced significant intolerance". Examples of significant intolerance were moved from the criteria to a Note. For the criterion that addresses if the patient has a pre-existing gastrointestinal medical condition, examples were moved from the criteria to a Note. For the criterion that addresses severe renal impairment, the example provided of creatinine clearance < 35 mL/min was moved from the criteria to a Note. **Osteoporosis Treatment for a Postmenopausal Patient.** Regarding the approval duration, wording was changed from "Approve for up to 2 years (total)" to "approve for 2 years". The criteria which stated that "Use of teriparatide and/or Tymlos does not exceed 2 years during a patient's lifetime" was changed to "approve use of teriparatide exceeding 2 years during a patient's lifetime if the patient is at high risk for fracture as determined by the prescriber." Examples of high fracture risk are provided in a Note. The criteria that requires low bone mass had the definition moved from the criteria to a Note. Wording for the criterion regarding inadequate response to an oral bisphosphonate was changed to "experienced inadequate efficacy". Examples of inadequate efficacy to an oral bisphosphonate were moved from the criteria to a Note. Wording of the criterion regarding intolerability to an oral bisphosphonate was changed to "experienced significant intolerance". Examples of significant intolerance were moved from the criteria to a Note. For the criterion that addresses if the patient has a pre-existing gastrointestinal medical condition, examples were moved from the criteria to a Note. For the criterion that addresses severe renal impairment, the example provided of creatinine clearance < 35 mL/min was moved from the criteria to a Note. **Osteoporosis (to Increase Bone Mass) in Men with Primary or Hypogonadal Osteoporosis.** Regarding the approval duration, wording was changed from "Approve for up to 2 years (total)" to "approve for 2 years". The criteria which stated that "Use of teriparatide and/or Tymlos does not exceed 2 years during a patient's lifetime" was changed to "approve use of teriparatide exceeding 2 years during a patient's lifetime if the patient is at high risk for fracture as determined by the prescriber." Examples of high fracture risk are provided in a Note. The criteria that requires low bone mass had the definition moved from the criteria to a Note. Wording for the criterion regarding inadequate response to an oral bisphosphonate was changed to "experienced inadequate efficacy". Examples of inadequate efficacy to an oral bisphosphonate were moved from the criteria to a Note. Wording of the criterion regarding intolerability to an oral bisphosphonate was changed to "experienced significant intolerance". Examples of significant intolerance were moved from the criteria	02/24/2021

	to a Note. For the criterion that addresses if the patient has a preexisting gastrointestinal medical condition, examples were moved from the criteria to a Note. For the criterion that addresses severe renal impairment, the example provided of creatinine clearance < 35 mL/min was moved from the criteria to a Note. **Hypoparathyroidism:** Regarding the approval duration, wording was changed from "Approve for up to 2 years (total)" to "approve for 2 years".	

PRIOR AUTHORIZATION POLICY

POLICY: Bone Modifiers – Tymlos Prior Authorization Policy

- Tymlos® (abaloparatide injection for subcutaneous use – Radius Health)

REVIEW DATE: 07/29/2020

OVERVIEW

Tymlos, a human parathyroid hormone related peptide (PTHrP[1-34]) analog, is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture.[1] Patients at high risk for fracture are defined as those with a history of osteoporotic fractures, have multiple risk factors for fracture, or have failed or are intolerant to other osteoporosis therapy.

Guidelines

Guidelines for osteoporosis in postmenopausal women from the Endocrine Society (2019)[2] as well as from the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) [2020][3] discuss Tymlos. In general, Tymlos is one of several alternatives recommended in patients who are at high risk of fracture or in those unable to utilize oral bisphosphonate therapy.

Safety

The prescribing information for Tymlos includes a Boxed Warning regarding an increased incidence of osteosarcoma in rats at doses 4 to 28 times the exposure in humans administered as a 80 mcg dose.[1] Due to these risks, the agent should not be given to those who have an increased baseline risk for osteosarcoma. The prescribing information for Tymlos states that cumulative use of Tymlos and parathyroid hormone analogs (e.g., teriparatide injection for subcutaneous use [Forteo®/Bonsity®]) for > 2 years during a patient's lifetime is not recommended.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Tymlos. Coverage cumulative with Tymlos and teriparatide injection for subcutaneous use (Forteo/Bonsity) is recommended for up to 2 years of a patient's lifetime. All approval(s) are provided for up to 2 years in duration unless otherwise noted below.

Automation: Smart Coverage Review uses patient claim history to answer Prior Authorization questions regarding medication history of Boniva® (ibandronate injection for intravenous use) or Reclast® (zoledronic acid injection for intravenous use). A 2-year look back period will be used to check claim history and automate for use of either agent (Boniva intravenous or Reclast). If not in claims, medication history can be obtained through Prior Authorization criteria. For all reviews, other Prior Authorization criteria listed below will also be applied.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Tymlos is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Osteoporosis Treatment for a Postmenopausal Patient.** Approve for up to 2 years (total) if the patient meets the following criteria (A, B, and C):
   - **D)** Patient meets ONE of the following conditions (i, ii, or iii):
     - **iv.** Patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip and/or 33% (one-third) radius (wrist); OR
     - **v.** Patient has had an osteoporotic fracture or a fragility fracture; OR
     - **vi.** The patient meets both of the following (a and b):
       - **a)** Patient has low bone mass (T-score [current or at any time in the past] between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip and/or 33% [one-third] radius [wrist]); AND
       - **b)** Prescriber determines the patient is at high risk for fracture; AND
   - **E)** Patient meets ONE of the following (i, ii, iii, or iv):
     - **vi.** Patient has tried ibandronate injection (Boniva) or zoledronic acid injection (Reclast); OR
     - **vii.** Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a, b, or c):

       Note: Examples of oral bisphosphonate products include Fosamax® (alendronate tablets and oral solution), Fosamax® Plus D (alendronate/cholecalciferol tablets), Actonel® (risedronate tablets), Atelvia® (risedronate delayed-release tablets), and Boniva® (ibandronate tablets).
       - **d)** Patient has had an inadequate response to oral bisphosphonate therapy after a trial duration of 12 months as determined by the prescriber (e.g., ongoing and significant loss of bone mineral density [BMD], lack of BMD increase); OR
       - **e)** Patient has had an osteoporotic fracture or fragility fracture while receiving oral bisphosphonate therapy; OR
       - **f)** Patient has experienced intolerability to an oral bisphosphonate (e.g., severe gastrointestinal [GI]-related adverse effects, severe musculoskeletal-related side effects, a femoral fracture); OR
     - **viii.** The patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):
       - **a)** Patient cannot swallow or has difficulty swallowing; OR
       - **b)** Patient cannot remain in an upright position post oral bisphosphonate administration; OR
       - **c)** Patient has a pre-existing gastrointestinal (GI) medical condition (e.g., patient with esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying [stricture, achalasia]); OR
     - **ix.** Patient meets one of the following conditions (a, b, or c):
       - **d)** Severe renal impairment (creatinine clearance < 35 mL/min); OR
       - **e)** Chronic kidney disease (CKD); OR
       - **f)** Patient has had an osteoporotic fracture or a fragility fracture; AND
   - **F)** Use of Tymlos and/or teriparatide injection for subcutaneous use (Forteo/Bonsity) does not exceed 2 years during a patient's lifetime.

     Note: Approve the duration necessary to complete a maximum of 2 years of therapy during a patient's lifetime (e.g., a patient who has already received 3 months of treatment with Tymlos or teriparatide [Forteo/Bonsity] should be approved for a duration of 21 months. This allows for completion of a maximum of 2 years of therapy).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tymlos is not recommended in the following situations:

61. Concurrent Use with Other Medications for Osteoporosis.
Note: Examples include Prolia® (denosumab injection for subcutaneous use), oral bisphosphonates (alendronate, risedronate, ibandronate), intravenous bisphosphonates (zoledronic acid injection [Reclast], ibandronate intravenous), calcitonin nasal spray (Miacalcin®/Fortical®), teriparatide injection for subcutaneous use (Forteo®/Bonsity), and Evenity® (romosozumab-aqqg injection for subcutaneous use). Tymlos is not indicated for use as combination therapy.

62. Osteoporosis Prevention. Tymlos has not been studied in this patient population. The benefits and risks of building bone with Tymlos in a condition in which substantial bone loss has not occurred have not been investigated.[1]

63. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

173. Tymlos® injection for subcutaneous use [prescribing information]. Waltham, MA: Radius Health; October 2018.
174. Eastell R, Rosen CJ, Black DM, et al. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2019;104(5):1595-1622.
175. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis-2020 update. *Endocrin Pract*. 2020;26(Suppl 1):1-46.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision.	No criteria changes.	06/20/2018
Annual revision	The following criteria changes were made: **Osteoporosis Treatment for a Postmenopausal Patient.** Criteria were added that use of Tymlos and/or Forteo does not exceed 2 years during a patient's lifetime. **Conditions Not Recommended for Approval.** The stipulation that use of Tymlos and/or Forteo does not exceed 2 years during a patient's lifetime was removed as this is now addressed in the approval conditions. Also, added Evenity to the list of medications that should not be used concomitantly with Tymlos.	07/03/2019
Annual revision	In related criteria the word "prescriber" is replacing the word/phrase "physician" or "prescribing physician". Additionally, the following changes were made: **Automation:** Automation was previously listed as "None". Smart Coverage Rule Automation was added. **Conditions Not Recommended for Approval:** For the criteria regarding Concurrent Use of Other Medications for Osteoporosis, the examples of other medications used for osteoporosis in the note were revised. Reference to calcium and vitamin D was deleted.	07/29/2020
Update	08/29/2020: No criteria changes: For the conditions that require a trial of at least one oral bisphosphonate or an oral bisphosphonate-containing product (osteoporosis treatment for a postmenopausal patient), added a note that provided examples of these products (Note: Examples of oral bisphosphonate products include Fosamax® [alendronate tablets and oral solution], Fosamax® Plus D [alendronate/cholecalciferol tablets], Actonel® [risedronate tablets], Atelvia® [risedronate delayed-release tablets], and Boniva® [ibandronate tablets]).	--

PRIOR AUTHORIZATION POLICY

POLICY: Bone Modifiers – Xgeva Prior Authorization Policy
- Xgeva® (denosumab injection for subcutaneous use – Amgen)

REVIEW DATE: 03/03/2021

OVERVIEW

Xgeva, a receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor, is indicated for the following uses[1]:

- **Giant cell tumor of bone**, treatment of adults and skeletally mature adolescents with disease that is unresectable or where surgical resection is likely to result in severe morbidity.
- **Hypercalcemia of malignancy** that is refractory to bisphosphonate therapy.
- **Skeletal-related events**, prevention of, in patients with multiple myeloma and in those with bone metastases from solid tumors.

Another injectable formulation of denosumab is available, Prolia®, but it is not included in this policy.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Xgeva. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Xgeva as well as the monitoring required for adverse events and long-term efficacy, approval requires Xgeva to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xgeva is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Bone Metastases from Solid Tumors – Prevention of Skeletal-Related Events.** Approve for 1 year if the patient meets the following criteria (A, B, C and D):
   Note: Some examples of cancer in this clinical scenario include breast cancer, prostate cancer, and non-small cell lung cancer.
   A) Patient is ≥ 18 years of age; AND
   B) Patient has bone metastases; AND
   C) Patient with prostate cancer must have received at least one hormonal therapy; AND
   Note: Examples of hormonal therapies for prostate cancer include Lupron Depot® (leuprolide for depot suspension), Eligard® (leuprolide acetate for injectable suspension), Trelstar® (triptorelin pamoate for injectable suspension), or Zoladex® (goserelin implant).
   D) The medication is prescribed by or in consultation with a hematologist or an oncologist.

2. **Giant Cell Tumor of Bone.** Approve for 1 year.
3. **Hypercalcemia of Malignancy.** Approve for 2 months if the patient meets the following criteria (A, B, and C):
   A) Patient has a current malignancy; AND
   B) Patient meets one of the following (i or ii):
   i. Patient has tried at least one intravenous (IV) bisphosphonate therapy; OR

Note: Examples include zoledronic acid injection (Zometa) and pamidronate injection (Aredia); OR

ii. Patient has an estimated calculated creatinine clearance (CrCl) < 30 mL/min; AND

C) Patient has an albumin-corrected calcium (cCa) ≥ 11.5 mg/dL.

4. Multiple Myeloma – Prevention of Skeletal-Related Events. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient is ≥ 18 years of age; AND

B) Medication is prescribed by or in consultation with a hematologist or an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xgeva is not recommended in the following situations:

14. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

75. Xgeva® injection for subcutaneous use [prescribing information]. Thousand Oaks, CA: Amgen; June 2020.
76. Prolia® injection for subcutaneous use [prescribing information]. Thousand Oaks, CA: Amgen; March 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	02/27/2019
Annual Revision	No criteria changes.	02/26/2020
Annual Revision	The following changes were made: **1. Bone Metastases from Solid Tumors – Prevention of Skeletal-Related Events:** The examples of breast cancer, prostate cancer, and non-small-cell lung cancer were moved as examples of cancers from the cited indication to a Note. Regarding the criterion that patients with prostate cancer must have received at least one hormonal therapy, the examples of hormonal therapies for prostate cancer were moved from the criteria to a Note. **2. Hypercalcemia of Malignancy:** Regarding the criteria that the patient has tried intravenous bisphosphonate therapy, the qualifier of "at least one" bisphosphonate therapy was added and examples were moved from the criteria to a Note.	03/03/2021

PRIOR AUTHORIZATION POLICY

POLICY: Bone Modifiers – Zoledronic Acid (Reclast) Prior Authorization Policy

- Reclast® (zoledronic acid injection – Novartis, generic)

REVIEW DATE: 03/03/2021

OVERVIEW

Zoldedronic acid (Reclast), a bisphosphonate given intravenously, is indicated for the following uses:[1]

- **Glucocorticoid-induced osteoporosis**, for treatment and prevention in men and women who are either initiating or continuing systemic glucocorticoids (e.g., prednisone 7.5 mg or greater) and who are anticipated to remain on glucocorticoids for at least 12 months.
- **Osteoporosis, prevention in postmenopausal women**.
- **Osteoporosis, treatment in men** to increase bone mass.
- **Osteoporosis, treatment in postmenopausal women.**
- **Paget's disease of bone**, treatment in men and women.

Another zoledronic acid injection product, Zometa®, is indicated for hypercalcemia of malignancy; and for multiple myeloma and bone metastases from solid tumors.[2] Although not indicated, zoledronic acid injection (Reclast) has been used in patients, mainly children, with osteogenesis imperfecta and benefits were noted, such as increases in bone mineral density.[1,3-8]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of zoledronic acid injection (Reclast). All approvals are provided for the duration noted below. In the approval indication for zoledronic acid injection (Reclast), as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indications

1. **Glucocorticoid-Induced Osteoporosis (GIO) – Prevention and Treatment.** Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient is either initiating or continuing systemic glucocorticoids; AND
     Note: An example of a systemic glucocorticoid is prednisone.
   - **B)** Patient meets ONE of the following (i, ii, iii, or iv):
     - **i.** Patient has tried zoledronic acid injection (Reclast); OR
     - **ii.** Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a, b, or c):
       Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).
       - **a)** According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months ; OR
         Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD) and lack of a BMD increase.
       - **b)** Patient has had an osteoporotic fracture or fragility fracture while receiving oral bisphosphonate therapy; OR
       - **c)** Patient has experienced significant intolerance to an oral bisphosphonate; OR
         Note: Examples of significant intolerance include severe gastrointestinal related adverse events, severe musculoskeletal related adverse events, and femoral fracture.
     - **iii.** Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):

a) Patient cannot swallow or has difficulty swallowing; OR
b) Patient cannot remain in an upright position post-oral bisphosphonate administration; OR
c) Patient has a pre-existing gastrointestinal medical condition in which intravenous bisphosphonate therapy may be warranted; OR
Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, and abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).

iv. Patient has had an osteoporotic fracture or a fragility fracture.

2. Osteoporosis – Prevention for a Postmenopausal Patient. Approve for 1 year if the patient meets the following criteria (A, B, and C):

A) Patient meets ONE of the following conditions (i or ii):
i. Patient has had a T-score (current or at any time in the past) between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one third) radius (wrist); OR
ii. Patient has had an osteoporotic fracture or a fragility fracture; AND

B) Patient meets ONE of the following (i, ii, iii, or iv):
i. Patient has tried zoledronic acid injection (Reclast); OR
ii. Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a, b, or c):
Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).
a) According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months ; OR
Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD) and lack of a BMD increase.
b) Patient has had an osteoporotic fracture or fragility fracture while receiving oral bisphosphonate therapy; OR
c) Patient has experienced significant intolerance to an oral bisphosphonate; OR
Note: Examples of significant intolerance include severe gastrointestinal related adverse events, severe musculoskeletal related adverse events, and femoral fracture.
iii. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):
a) Patient cannot swallow or has difficulty swallowing; OR
b) Patient cannot remain in an upright position post oral bisphosphonate administration; OR
c) Patient has a pre-existing gastrointestinal medical condition in which intravenous bisphosphonate therapy may be warranted; OR
Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, and abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).
iv. Patient has had an osteoporotic fracture or a fragility fracture; AND

C) If the patient has received Reclast previously, at least 24 months has elapsed since the last dose.

3. Osteoporosis – Treatment for Men*. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient meets ONE of the following conditions (i, ii, or iii):
i. Patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one third) radius (wrist); OR
ii. Patient has had an osteoporotic fracture or a fragility fracture; OR
iii. Patient meets both of the following (a and b):
a. Patient has low bone mass; AND

Note: An example of low bone mass includes a T-score (current or at any time in the past) between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip and/or 33% (one-third) radius (wrist).

b. According to the prescriber, patient is at high risk for fracture; AND

B) Patient meets ONE of the following (i, ii, iii, or iv):

i. Patient has tried zoledronic acid injection (Reclast); OR

ii. Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a, b, or c):

Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).

a) According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR

Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD) and lack of a BMD increase.

b) Patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy; OR

c) Patient has experienced significant intolerance to an oral bisphosphonate; OR

Note: Examples of significant intolerance include severe gastrointestinal related adverse events, severe musculoskeletal related adverse events, and femoral fracture.

iii. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):

a) Patient cannot swallow or has difficulty swallowing; OR

b) Patient cannot remain in an upright position post oral bisphosphonate administration; OR

c) Patient has a pre-existing gastrointestinal medical condition in which intravenous bisphosphonate therapy may be warranted; OR

Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, and abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).

iv. Patient has had an osteoporotic fracture or a fragility fracture.

***** Refer to the Policy Statement.

4. Osteoporosis – Treatment for a Postmenopausal Patient. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient meets ONE of the following conditions (i, ii, or iii):

i. Patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius (wrist); OR

ii. Patient has had an osteoporotic fracture or a fragility fracture; OR

iii. Patient meets both of the following (a and b):

a) Patient has low bone mass; AND

Note: An example of low bone mass includes a T-score (current or at any time in the past) between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip and/or 33% (one-third) radius (wrist).

b) According to the prescriber, patient is at high risk for fracture; AND

B) Patient meets ONE of the following (i, ii, iii, or iv):

i. Patient has tried ibandronate injection (Boniva IV) or zoledronic acid injection (Reclast); OR

ii. Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a, b, or c):

Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).

a) According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months ; OR
Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD) and lack of a BMD increase.

b) Patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy; OR

c) Patient has experienced significant intolerance to an oral bisphosphonate; OR
Note: Examples of significant intolerance include severe gastrointestinal related adverse events, severe musculoskeletal related adverse events, and femoral fracture.

iii. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):

a) Patient cannot swallow or has difficulty swallowing; OR

b) Patient cannot remain in an upright position post oral bisphosphonate administration; OR

c) Patient has a pre-existing gastrointestinal medical condition in which intravenous bisphosphonate therapy may be warranted; OR
Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, and abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).

iv. Patient has had an osteoporotic fracture or a fragility fracture.

5. Paget's Disease of Bone. Approve for one dose if the patient meets one of the following criteria (A, B, or C):

A) Patient has elevations in serum alkaline phosphatase of two times higher than the upper limit of the age-specific normal reference range; OR

B) Patient is symptomatic; OR
Note: Examples of symptoms include bone pain, hearing loss, and osteoarthritis.

C) Patient is at risk for complications from their disease.
Note: Examples of disease complications include immobilization, bone deformity, fractures and nerve compression syndrome.

Other Uses with Supportive Evidence

6. Osteogenesis Imperfecta. Approve for 1 year.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of zoledronic acid injection (Reclast) is not recommended in the following situations:

1. Concurrent Use of Zoledronic Acid Injection (Reclast) with Other Medications for Osteoporosis.
Note: Examples of other medications for osteoporosis include oral bisphosphonates (e.g., alendronate, risedronate, ibandronate), other intravenous bisphosphonates (e.g., intravenous ibandronate [Boniva]), Prolia (denosumab injection for subcutaneous use), Evenity [romosozumab-aqqg injection for subcutaneous use], Forteo (teriparatide injection for subcutaneous use, generic), Tymlos (abaloparatide injection for subcutaneous use), and calcitonin nasal spray.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Reclast® injection [prescribing information]. East Hanover, NJ: Novartis; April 2020.
2. Zometa® injection for intravenous infusion [prescribing information]. East Hanover, NJ: Novartis; December 2018.
3. Biggin A, Munns CF. Long-term bisphosphonate therapy in osteogenesis imperfecta. *Curr Osteoporos Rep*. 2017;15(5):412-418.
4. Barros ER, Saraiva GL, de Oliveira P, Lazaretti-Castro M. Safety and efficacy of a 1-year treatment with zoledronic acid compared with pamidronate in children with osteogenesis imperfecta. *J Pediatr Endocr Met*. 2012;25(5-6):485-491.
5. Panigrahi I, Das RR, Sharda S, et al. Response to zoledronic acid in children with type III osteogenesis imperfecta. *J Bone Miner Metab*. 2010;28:451-455.
6. Brown JJ, Zacharin MR. Safety and efficacy of intravenous zoledronic acid in paediatric osteoporosis. *J Pediatr Endocrinol Metab*. 2009;22(1):55-63.
7. Vuorimies I, Toiviainen-Salo S, Hero M, Makitie O. Zoledronic acid treatment in children with osteogenesis imperfecta. *Horm Res Paediatr*. 2011;75:346-353.
8. Dwan K, Phillipi CA, Steiner RD, Basel D. Bisphosphonate therapy for osteogenesis imperfecta. *Cochrane Database Syst Rev*. 2016;10:CD005088.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	In the Conditions Not Recommended for Approval section, added medication examples that Reclast should not be used with concomitantly (e.g., Bonsity, Evenity, and provided examples of bisphosphonates).	02/26/2020
Annual Revision	The following criteria changes were made: i. **Glucocorticoid-Induced Osteoporosis – Treatment:** The example of prednisone as a systemic glucocorticoid was moved from the criteria to a Note. Regarding the criterion that requires a trial of one oral bisphosphonate, the wording was added to state "at least one". Examples of oral bisphosphonates are now provided in a Note. Wording for the criterion regarding inadequate response to an oral bisphosphonate was changed to "experienced inadequate efficacy". For this criterion, "prescribing physician" was changed to "prescriber". Examples of inadequate efficacy to an oral bisphosphonate were moved from the criteria to a Note. Wording of the criterion regarding intolerability to an oral bisphosphonate was changed to "experienced significant intolerance". Examples of significant intolerance were moved from the criteria to a Note. For the criterion that addresses if the patient has a pre-existing gastrointestinal medical condition, examples were moved from the criteria to a Note. i. **Osteoporosis – Prevention for a Postmenopausal Patient:** Regarding the criterion that requires a trial of one oral bisphosphonate, the wording was added to state "at least one". Examples of oral bisphosphonates are now provided in a Note. Wording for the criterion regarding inadequate response to an oral bisphosphonate was changed to "experienced inadequate efficacy". For this criterion, "prescribing physician" was changed to "prescriber". Examples of inadequate efficacy to an oral bisphosphonate were moved from the criteria to a Note. Wording of the criterion regarding intolerability to an oral bisphosphonate was changed to "experienced significant intolerance". Examples of significant intolerance were moved from the criteria to a Note. For the criterion that addresses if the patient has a pre-existing gastrointestinal medical condition, examples were moved from the criteria to a Note. i. **Osteoporosis – Treatment for Men.** The criteria that requires low bone mass had the definition moved from the criteria to a Note. Also, the wording that the "prescribing physician" had to make this determination was changed to state "prescriber". Regarding the criterion that requires a trial of one oral bisphosphonate, the wording was added to state "at least one". Examples of oral bisphosphonates are now provided in a Note. Wording for the criterion regarding inadequate response to an oral bisphosphonate was changed to "experienced inadequate efficacy". For this criterion, "prescribing physician" was changed to "prescriber". Examples of inadequate efficacy to an oral bisphosphonate were moved from the criteria to a Note. Wording of the criterion regarding intolerability to an oral bisphosphonate was changed to "experienced significant intolerance". Examples of significant intolerance were moved from the criteria to a Note. For the criterion that addresses if the patient has a pre-existing gastrointestinal medical condition, examples were moved from the criteria to a Note. v. **Osteoporosis – Treatment for a Postmenopausal Patient:** The criteria changes were the same at those noted above for the indication of "Osteoporosis – Treatment for Men". v. **Paget's Disease:** For the criteria that requires that the patient is symptomatic, examples were moved from the criteria to a Note. For the criteria that requires that the patient is at risk for complications of their disease, the examples were moved from the criteria to a Note. i. **Other Conditions Not Recommended for Approval:** For the notation cited regarding "Concurrent Use of Zoledronic Acid Injection (Reclast) with Other Medications for Osteoporosis" the examples of medications were moved from the criteria to a Note; the medication list was revised. Also, the wording stating "except calcium and vitamin D" was removed.	03/03/2021

PRIOR AUTHORIZATION POLICY

POLICY: Bone Modifiers – Zoledronic Acid (Zometa) Prior Authorization Policy
- Zometa® (zoledronic acid injection – Novartis, generic)

REVIEW DATE: 03/03/2021

OVERVIEW

Zoledronic acid injection (Zometa), a bisphosphonate, is indicated for the treatment of the following:[1]
- **Hypercalcemia of malignancy**.
- **Multiple myeloma and documented bone metastases from solid tumors**, in addition to standard antineoplastic therapy.

Prostate cancer should have progressed after treatment with at least one hormonal therapy.[1] Another formulation of zoledronic acid injection is available, Reclast®, but is not included in this policy.[2]

Other Uses With Supportive Evidence

Data are available with zoledronic acid injection (Zometa) regarding off-label uses. One example is to prevent bone loss in patients with breast cancer receiving aromatase inhibitor therapy. Aromatase inhibitor therapy prevents peripheral production and suppress estrogen levels and can lead to accelerated bone loss beyond what would naturally occur in women.[3,4] This can place the patient at an increased risk for having a fracture. A review on the management of aromatase inhibitor-associated bone loss in postmenopausal women with breast cancer[5] states that zoledronic acid injection (Zometa) [4 mg every 6 months] is the preferred agent for prevention and treatment of aromatase inhibitor bone loss.[4] Zoledronic acid injection (Zometa) has been studied and shown benefits in postmenopausal women receiving adjuvant letrozole for breast cancer.[5,6]

Zoledronic acid injection (Zometa) has also been utilized to prevent bone loss in patients with prostate cancer who are receiving androgen deprivation therapy (ADT). ADT is associated with a variety of adverse events, including osteoporosis. The National Comprehensive Cancer Network (NCCN) clinical practice guidelines regarding prostate cancer (version 2.2021 – February 17, 2021)[7] cite zoledronic acid as an option to increase bone density, a surrogate for fracture risk, during ADT for prostate cancer. Zoledronic acid injection (Zometa) has led to bone mineral density increases in patients with prostate cancer who are receiving androgen deprivation therapy.[8,9] A clinical practice guideline for osteoporosis in men from the Endocrine Society[9] recommends pharmacological treatment for osteoporosis for men with prostate cancer receiving ADT who have a high risk of fracture.

Zoldedronic acid injection (Zometa) has utility in premenopausal patients with breast cancer who have developed ovarian failure. Chemotherapy-induced ovarian failure is an adverse effect associated with some adjuvant chemotherapy and can lead to rapid bone loss.[10,11] Studies have demonstrated zoledronic acid injection (Zometa) to be efficacious in preserving bone mineral density in premenopausal women with breast cancer who developed ovarian failure due to adjuvant chemotherapy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of zoledronic acid injection (Zometa). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with zoledronic acid injection (Zometa) as well as the monitoring required for adverse events and long-term efficacy, approval requires zoledronic acid injection (Zometa) to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of zoledronic acid injection (Zometa) is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Bone Metastases From Solid Tumors – Treatment** Approve for 1 year if the patients meets all of the following criteria (A, B, and C):
   Note: Some examples of cancer in this clinical scenario include breast cancer, prostate cancer, non-small cell lung cancer, renal cell cancer, small cell lung cancer, colorectal cancer, bladder cancer, gastrointestinal/genitourinary cancer, and head and neck cancer.
   A) Patient has bone metastases; AND
   B) Patient with prostate cancer must have received at least one hormonal therapy; AND
   Note: Examples of hormonal therapies for prostate cancer include Lupron Depot® (leuprolide for depot suspension), Eligard® (leuprolide acetate for injectable suspension), Trelstar® (triptorelin pamoate for injectable suspension), and Zoladex® (goserelin implant).
   C) The medication is prescribed by or in consultation with a hematologist or an oncologist.

2. **Hypercalcemia of Malignancy.** Approve for 1 month if the patient meets the following criteria (A and B):
   A) Patient has a current malignancy; AND
   B) Patient has an albumin-corrected calcium (cCa) ≥ 11.5 mg/dL.

3. **Multiple Myeloma – Treatment.** Approve for 1 year if the agent is prescribed by or in consultation with a hematologist or an oncologist.

Other Uses with Supportive Evidence

4. **Prevention of Bone Loss (To Increase Bone Mass) in Patients with Breast Cancer Receiving Aromatase Inhibitor Therapy**. Approve for 1 year if the patient meets the following criteria (A and B):
   A) Patient has breast cancer that is not metastatic to bone; AND
   B) Patient is receiving an aromatase inhibitor therapy.
   Note: Examples of aromatase inhibitor agents include anastrozole, letrozole, and exemestane.

5. **Prevention of Bone Loss (To Increase Bone Mass) in Patients with Prostate Cancer Who are Receiving Androgen Deprivation Therapy (ADT).** Approve for 1 year if the patient meets the following criteria (A and B):
   A) Patient has prostate cancer that is not metastatic to bone; AND
   B) Patient must meet one of the following (i or ii):
      i. Patient is currently receiving androgen deprivation therapy; OR
      Note: Examples of androgen deprivation therapies include Lupron Depot® (leuprolide for depot suspension), Eligard® (leuprolide acetate for injectable suspension), Trelstar® (triptorelin pamoate for injectable suspension), or Zoladex® (goserelin implant).
      ii. Patient has undergone bilateral orchiectomy.

6. **Prevention of Bone Loss (to Increase Bone Mass) in Premenopausal Patients with Breast Cancer Who Have Developed Ovarian Failure.** Approve for 1 year if the patient meets the following criteria (A, B and C):
   A) Patient is premenopausal; AND
   B) Breast cancer is not metastatic to bone; AND
   C) Patient received adjuvant chemotherapy that led to ovarian failure.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of zoledronic acid (Zometa) is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	03/06/2019
Annual Revision	No criteria changes.	02/26/2020
Annual Revision	The following changes were made: **1. Bone Metastases from Solid Tumors – Treatment:** The examples of cancers were moved from the cited indication to a Note. Regarding the criterion that patients with prostate cancer must have received at least one hormonal therapy, the examples of hormonal therapies for prostate cancer were moved from the criteria to a Note. **2. Prevention of Bone Loss (To Increase Bone Mass) in Patients with Breast Cancer Receiving Aromatase Inhibitor Therapy**. The examples of aromatase inhibitor therapies were moved from the criteria to a Note. **3. Prevention of Bone Loss (To Increase Bone Mass) in Patients with Prostate Cancer Who are Receiving Androgen Deprivation Therapy (ADT).** The examples of androgen deprivation therapies were moved from the criteria to a Note.	03/03/2021

PRIOR AUTHORIZATION POLICY

POLICY: Botulinum Toxins – Botox Prior Authorization Policy

- Botox® (onabotulinumtoxinA for injection – Allergan)

REVIEW DATE: 06/03/2020; selected revision 02/24/2021

OVERVIEW

Botox, a botulinum toxin, is indicated for the following:

- **Blepharospasm** associated with dystonia, including benign essential blepharospasm or seventh nerve disorders, and strabismus in patients ≥ 12 years of age.
- **Cervical dystonia,** to reduce the severity of abnormal head position and neck pain associated with cervical dystonia.
- **Hyperhidrosis, primary axillary**, that is inadequately treated with topical agents.
- **Migraine headache prophylaxis,** in adults with chronic migraine (≥ 15 days per month with headache lasting 4 hours per day or longer).
- **Overactive bladder** with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have inadequate response to or are intolerant of an anticholinergic medication.
- **Spasticity** (upper and lower limb) in patients ≥ 2 years of age.
- **Urinary incontinence due to detrusor overactivity** associated with a neurological condition (e.g., spinal cord injury, multiple sclerosis) in adults who have an inadequate response to or are intolerant of an anticholinergic medication.
- **Neurogenic detrusor overactivity** in pediatric patients ≥ 5 years of age who have had an inadequate response to or are intolerant of an anticholinergic medication.[1]

In addition, botulinum toxin type A has been used to treat a multitude of disorders characterized by abnormal muscle contraction.[2] The benefit of this drug has also been demonstrated in the treatment of gastrointestinal, genitourinary, ocular, and autonomic nervous system disorders.[2,3] Of note, with regard to the indication of migraine headache prophylaxis, an updated assessment of the preventive and acute treatment of migraine by the American Headache Society (2018) notes that all patients with migraine should be offered a trial of acute treatment.[4] Regarding migraine prophylaxis, several medications are cited as having established or probable efficacy in migraine prevention, including antiepileptic medications, beta-blockers, antidepressants, and Botox.

Other Uses with Supportive Evidence

Botox has been studied in a variety of indications outside of FDA-approved uses. Literature is available to support use of Botox in the following conditions:

- **Achalasia:** The American College of Gastroenterology (ACG) clinical guideline for the diagnosis and management of achalasia (2013) recommends the use of botulinum toxin therapy in patients who are not good candidates for more definitive therapy with pneumatic dilation or surgery (myotomy).[5]
- **Anal Fissures:** The ACG clinical guideline for the management of benign anorectal disorders (2014) recommends the use of botulinum toxin therapy or surgical internal anal sphincterotomy in patients who do not respond to conservative or topical pharmacologic agents, such as a calcium channel blockers or nitrates.[6]
- **Chronic Facial Pain/Pain Associated with Temporomandibular Dysfunction:** Data from several open-label studies, as well as one randomized, placebo-controlled trial, support the efficacy of Botox in the treatment of chronic facial pain/chronic facial pain associated with hyperactivity of the masticatory muscles.[7-10]
- **Chronic Low Back Pain:** In one 8-week, randomized, double-blind, placebo-controlled trial in 31 patients with chronic low back pain (no causative factor identified in the majority of patients; history of disc disease in 6 patients, discectomy in 3 patients, and trauma in 4 patients), Botox in addition to their current pharmacologic treatment regimen resulted in significantly greater improvement in pain relief and degree of disability compared with placebo.[11] A 14-month, open-label, prospective study evaluated the short- and long-term effects of paraspinal muscle injections

of Botox in 75 patients with refractory chronic low back pain. A total of 53% and 52% of patients reported significant pain relief at 3 weeks and 2 months, respectively.[12]

- **Dystonia, other than cervical (e.g., focal dystonias, tardive dystonia, anismus, laryngeal dystonia/spasmodic dysphonia):** Guidelines from the American Academy of Neurology (AAN) support use of botulinum toxins in focal dystonias of the upper extremity (should be considered; Level B recommendation).[13] Botulinum toxin A is the most widely accepted treatment for spasmodic dysphonia, a focal laryngeal dystonia, viewed as the treatment of choice by the American Academy of Otolaryngology-Head and Neck Surgery.[14] Per the guideline, clinicians should offer, or refer to a clinician who can offer, botulinum toxin injections for treatment of dysphonia caused by spasmodic dysphonia and other types of laryngeal dystonia. AAN guidelines note that botulinum toxin is probably effective and should be considered for adductor type laryngeal dystonia (Level B).[13]
- **Essential Tremor:** According to the clinical practice parameter on essential tremor by the AAN, propranolol and primidone are first-line therapy in the treatment of essential tremor.[15] Second-line medication options include alprazolam, atenolol, (monotherapy), sotalol, gabapentin, and topiramate. Botulinum toxin A may also reduce tremor. The guidelines recommend that botulinum toxin A may be considered in medically refractory cases of limb, head, and voice tremor associated with essential tremor (Level C for limb, head, and voice tremor).
- **Frey's Syndrome (gustatory sweating):** AAN guidelines state that botulinum toxin may be considered for this use (Level C). Botox is recommended as a first-line option for Frey's syndrome by the International Hyperhidrosis Society.[16,17]
- **Hyperhidrosis, Palmar/Plantar and Facial:** The efficacy of Botox is well-established in the treatment of primary focal/palmar hyperhidrosis based on data from both randomized, double-blind, placebo-controlled studies and open-label studies.[3,18,19] Guidelines from the International Hyperhidrosis Society support use of Botox in patients who have failed to respond to topical therapy.[16,20,21] AAN guidelines state that botulinum toxins are probably safe and effective and should be considered for palmar hyperhidrosis (plantar and facial hyperhidrosis are not addressed in the AAN guideline).[17]
- **Myofascial Pain:** Data from several retrospective reviews and open-label trials support the efficacy of Botox in the treatment of myofascial pain syndromes associated with various muscle groups.[7,22] In one randomized, controlled trial in 40 patients with chronic myofascial pain of various forms, Botox resulted in a significantly greater reduction in pain score from baseline compared with intramuscularly administered methylprednisolone at 30 days and 60 days post injection.[23] Another double-blind, randomized, placebo-controlled study involving 30 patients showed no difference in spontaneous and evoked pain reduction between Botox and isotonic saline injection recipients.[24]
- **Ophthalmic Disorders, Other Than Blepharospasm or Strabismus (e.g., esotropia, exotropia, nystagmus, facial nerve paresis):** Botulinum toxin A has been successful in improving or treating many ophthalmic disorders. One retrospective review (n = 54) concluded that Botox may have a role in the treatment of esotropia in patients > 18 months of age.[25] Botox improved visual acuity in one small, open-label study in patients with acquired symptomatic nystagmus from multiple sclerosis or brain-stem hemorrhage as well as in case reports.[26,27] Data from uncontrolled studies have shown Botox to be beneficial in the treatment of sixth nerve palsy.[28,29]
- **Plantar Fasciitis:** In one randomized, double-blind study (n = 36), botulinum toxin A exhibited more rapid and sustained improvement over the duration of the study as compared with the patients who received steroid injections.[30] The clinical consensus statement on the diagnosis and treatment of heel pain (developed by the American College of Foot and Ankle Surgeons) published in 2010, botulinum toxin injection is listed as a Tier 2 option (Grade I); Tier 1 treatment options include: padding and strapping of the foot (Grade B), therapeutic orthotic insoles (Grade B), oral anti-inflammatory agents (Grade I), corticosteroid injections (Grade B), and Achilles and plantar fascia

stretching (Grade B) [Grade B recommendations are supported by fair evidence, Grade I recommendations indicate there is insufficient evidence to make a recommendation].[31]

- **Sialorrhea, Chronic:** Botulinum toxin A has been studied in the treatment of sialorrhea associated with Parkinson's Disease, parkinsonian syndromes, cerebral palsy, head and neck carcinoma, neurodegenerative disease, stroke, and amytrophic lateral sclerosis (ALS).[3] A review of the literature on medical treatment of sialorrhea found that Botox is probably effective for the treatment of this condition (level B evidence).[32] AAN guidelines note that botulinum toxin is probably safe and effective and should be considered (Level B).[17]
- **Spasticity, Other Than Lower and Upper Limb (i.e., spasticity or hypertonia due to cerebral palsy, stroke, brain injury, spinal cord injury, multiple sclerosis, hemifacial spasm):** Per the AAN, botulinum toxin is established effective in upper and lower limb spasticity and in cerebral palsy (Level A), and it may be considered in hemifacial spasm (Level C).[13,33]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Botox. Use should be limited to the treatment of medical conditions. Prescription benefit coverage of this product is not recommended for cosmetic conditions. All approvals are provided for 1 year. Previous therapy is required to be verified by a clinician in the Coverage Review Department when noted in the criteria as **[verification of therapies required]**.

Prior authorization and prescription benefit coverage are not recommended for Botox Cosmetic.

Automation: None

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indications

1. **Blepharospasm Associated with Dystonia or Strabismus**. Approve for 1 year.

2. **Cervical Dystonia (spasmodic torticollis).** Approve for 1 year.
   Note: Cervical dystonia is also known as spasmodic or cervical torticollis.

3. **Hyperhidrosis, Primary Axillary.** Approve for 1 year if the patient has tried at least one topical agent (e.g., topical aluminum chloride, Qbrexza™ [glycopyrronium cloth 2.4% for topical use]).

4. **Migraine Headache Prophylaxis in Patients with Chronic Migraine.** Approve for 1 year in patients who meet all of the following conditions (A, B, C, and D):
   - **A)** Patient has ≥ 15 migraine headache days per month with headache lasting 4 hours per day or longer (prior to initiation of Botox therapy); AND
   - **B)** Patient has tried at least two other prophylactic pharmacologic therapies, each from a different pharmacologic class (e.g., beta-blocker, anticonvulsant, tricyclic antidepressant) **[verification of therapies required]**; AND
   - **C)** Patient meets ONE of the following (i or ii):
     - **i.** Patient has tried at least one triptan therapy; OR
     - **ii.** Patient has a contraindication to triptan(s) according to the prescriber; AND
   - **D)** Botox is being prescribed by or after consultation with a neurologist or headache specialist.

5. **Overactive Bladder with Symptoms of Urge Urinary Incontinence, Urgency, and Frequency.** Approve for 1 year if the patient has tried at least one other pharmacologic therapy.
   Note: Examples of other pharmacologic therapies include a beta-3 adrenergic agonist or an anticholinergic medication. For treatment of urinary incontinence associated with a neurological condition (e.g., spinal cord injury, multiple sclerosis, spina bifida), see FDA-Approved Indications criterion #8 (below).

6. **Spasticity, Lower Limb**. Approve for 1 year.
   Note: For other forms of spasticity that do not fit this condition of approval, see Other Uses with Supportive Evidence, Spasticity.

7. **Spasticity, Upper Limb.** Approve for 1 year.
   Note: For other forms of spasticity that do not fit this condition of approval, see Other Uses with Supportive Evidence, Spasticity.

8. **Urinary Incontinence Associated with a Neurological Condition (e.g., spinal cord injury, multiple sclerosis, spina bifida).** Approve for 1 year if the patient has tried at least one other pharmacologic therapy.
   Note: Examples of other pharmacologic therapies include a beta-3 adrenergic agonist or an anticholinergic medication. For treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, see FDA-Approved Indications criterion #5 (above).

Other Uses with Supportive Evidence

9. **Achalasia**. Approve for 1 year.

10. **Anal Fissure (anal sphincter).** Approve for 1 year.

11. **Chronic Facial Pain/Pain Associated with Temporomandibular Dysfunction.** Approve for 1 year.

12. **Chronic Low Back Pain.** Approve for 1 year in patients who meet the following conditions (A and B):
    A) Patient has tried at least two other pharmacologic therapies (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], antispasmodics, muscle relaxants, opioids, antidepressants); AND
    B) Botox is being used as part of a multimodal therapeutic pain management program.[3]

13. **Dystonia, Other Than Cervical (e.g., focal dystonias, tardive dystonia, anismus, laryngeal dystonia/spasmodic dysphonia).** Approve for 1 year.
    Note: For cervical dystonia, see FDA-Approved Indications criterion #2 (above).

14. **Essential Tremor.** Approve for 1 year after a trial with at least one other pharmacologic therapy (e.g., primidone, propranolol, benzodiazepines, gabapentin, topiramate).

15. **Frey's Syndrome (gustatory sweating).** Approve for 1 year.

16. **Hyperhidrosis, Palmar/Plantar and Facial.** Approve for 1 year if the patient has tried at least one topical agent (e.g., aluminum chloride).

17. **Myofascial Pain.** Approve for 1 year.

18. **Ophthalmic Disorders, Other Than Blepharospasm or Strabismus (e.g., esotropia, exotropia, nystagmus, facial nerve paresis).** Approve for 1 year.
    Note: For blepharospasm associated with dystonia or strabismus, see FDA-Approved Indications criterion #1 (above).

19. **Plantar Fasciitis.** Approve for 1 year after a trial of two other treatment modalities (e.g., padding and strapping of the foot, therapeutic orthotic insoles, oral anti-inflammatory drugs, corticosteroid injections, stretching).

20. **Sialorrhea, Chronic.** Approve for 1 year.

21. **Spasticity, Other Than Lower and Upper Limb (i.e., spasticity or hypertonia due to cerebral palsy, stroke, brain injury, spinal cord injury, multiple sclerosis, hemifacial spasm).** Approve for 1 year.
    Note: For lower and upper limb spasticity, see FDA-Approved Indications criteria #6 and #7 (above).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Botox is not recommended in the following situations:

1. **Cosmetic Uses** (e.g., facial rhytides, frown lines, glabellar wrinkling, horizontal neck rhytides, mid and lower face and neck rejuvenation, platsymal bands, rejuvenation of the periorbital region). Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical medical benefit.

2. **Fibromyalgia.** More data are needed to define the place in therapy of Botox in the treatment of fibromyalgia. A small pilot study involving 16 patients concluded botulinum toxin A injections into fibromyalgia trigger points offered more relief (up to 16 weeks minimum) compared with local saline or anesthetic injections; it was concluded Botox is effective in the treatment of fibromyalgia.[34] Other small studies have shown effectiveness of Botox in pain relief post injection.[2] Botox is not mentioned in guidelines for the treatment of fibromyalgia.

3. **Gastroparesis.** The ACG issued clinical guidelines on the management of gastroparesis (2013).[35] ACG does not recommend the use of botulinum toxin injected into the pylorus as a treatment for gastroparesis. This is based on two double-blind, placebo-controlled studies which did show some improvement in gastric emptying, but no improvement in symptoms compared with placebo.

4. **Vaginismus.** More data are needed to define the place in therapy of Botox in the treatment of vaginismus. The use of Botox for the treatment of vaginismus has been evaluated in a few small studies with successful outcomes.[36]

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Hyperhidrosis, Primary Axillary:** Qbrexza was added as an example of a medication that satisfies the requirement for trial of a topical product. **Ophthalmic Disorders, Other Than Blepharospasm or Strabismus:** "Other than blepharospasm or strabismus" added for clarification. Clarification noted to refer to FDA-Approved Indication #1 for Blepharospasm Associated with Dystonia or Strabismus. **Spasticity, Other Than Lower and Upper Limb:** "Other than lower or upper limb" added for clarification.	05/08/2019
Annual Revision	**FDA-Approved Uses:** • "Cervical Dystonia" updated to "Cervical Dystonia (spasmodic torticollis)". • Under criteria for "Migraine Headache Prophylaxis in Patients with Chronic Migraine", "prescribing physician" was updated to "prescriber". **Other Uses with Supportive Evidence:** • "Benign Prostatic Hyperplasia" removed from policy. • "Salivary Hypersecretion" updated to "Sialorrhea, Chronic." • "Speech/Voice Disorder (e.g., dysphonias)" renamed to laryngeal dystonia/spasmodic torticollis. This approval condition was rolled up into "Dystonia, other than cervical" and laryngeal dystonia/spasmodic dysphonia was added to the list of examples. • "Tinnitus" removed from policy.	06/03/2020
Selected Revision	**Overactive Bladder with Symptoms of Urge Urinary Incontinence, Urgency, and Frequency:** Examples of pharmacologic therapies were updated to "a beta-3 adrenergic agonist or an anticholinergic medication" and were moved from examples to a note. Specific product names were removed from the examples. **Urinary Incontinence Associated with a Neurological Condition (e.g., spinal cord injury, multiple sclerosis, spina bifida):** Spina bifida was added to the list of examples of neurological conditions. Examples of pharmacologic therapies were updated to "a beta-3 adrenergic agonist or an anticholinergic medication" and were moved from examples to a note. Specific product names were removed from the examples.	02/24/2021

PRIOR AUTHORIZATION POLICY

POLICY: Botulinum Toxins – Dysport® (abobotulinumtoxinA for injection – Ipsen)

DATE REVIEWED: 06/03/2020

OVERVIEW

Dysport® (abobotulinumtoxinA), is indicated for the following:

- Treatment of cervical dystonia in adults;
- Treatment of upper and lower limb spasticity in adults;
- Treatment of upper limb spasticity in pediatric patients ≥ 2 years of age, excluding spasticity caused by cerebral palsy; and
- Treatment of lower limb spasticity in pediatric patients ≥ 2 years of age.[1]

Toxin distribution varies between the commercially available botulinum toxin A products, Botox® (onabotulinumtoxinA), Xeomin® (incobotulinumtoxinA), and Dysport.[1-4] It has been postulated that differences in albumin concentration control diffusion of toxin from the injection site (Botox contains 500 mcg of albumin, while Dysport contains 125 mcg of albumin and Xeomin contains 1 mg of albumin). In addition, the labels for the botulinum toxin type A products (Botox, Dysport, and Xeomin) state that there

is a lack of interchangeability between the products for various reasons, including differences in the units of biological activity.[1,2,4] Studies have attempted to establish a conversion ratio between botulinum toxin products, with variable results. In general, conversion ratios of 1:1 for Botox to Xeomin, 1:3 for Botox to Dysport, and 1:50 to 1:100 for Botox to Myobloc have been suggested.[5,6]

Other Uses with Supportive Evidence

Botulinum toxins, including Dysport, have been studied in a variety of indications outside of FDA-approved uses. Literature is available to support use of Dysport in the following conditions:

- **Anal Fissure (anal sphincter):** There is an extensive amount of data from open-label studies, randomized, placebo-controlled trials, and randomized, comparative trials supporting the efficacy of botulinum toxin A in the treatment of anal fissures.[7-9] Injection of botulinum toxin allows healing in approximately 60% to 80% of anal fissures.[10] There is no consensus on the dose, site of injection, or number of injections. Botulinum toxin A has been shown to be more effective than topical nitroglycerin but less effective than surgery in inducing and maintaining fissure healing.[11] The ACG clinical guideline for the management of benign anorectal disorders (2014) recommends the use of botulinum toxin therapy or surgical internal anal sphincterotomy in patients who do not respond to conservative or topical pharmacologic agents, such as a calcium channel blockers or nitrates.[9]
- **Blepharospasm:** Dysport has demonstrated efficacy in clinical trials in patients with blepharospasm.[12,13] AAN guidelines (2016) support the use of Dysport for blepharospasm with a Level C recommendation ("possibly effective").[14]
- **Frey's Syndrome (gustatory sweating):** Botulinum toxin A has been successfully used to treat gustatory sweating. Dysport demonstrated efficacy in two small trials in a total of 53 patients with gustatory sweating.[15] American Academy of Neurology (AAN) guidelines state that botulinum toxin is possibly effective and may be considered for this use (Level C).[16]
- **Hyperhidrosis, Primary Axillary:** Topical antiperspirants (e.g., topical aluminum chloride) or Qbrexza are the recommended first-line therapy for the treatment of primary axillary hyperhidrosis.[17-20] The efficacy of Dysport for axillary hyperhidrosis was demonstrated in one randomized, double-blind, multicenter study in patients (n = 145) unresponsive to topical therapy with aluminum chloride (10% or 20%).[21] A significant ($P < 0.001$) decrease in sweat production vs. placebo occurred 2 weeks post-injection and was maintained 24 weeks post-injection.
- **Sialorrhea, Chronic:** Botulinum toxin A has been studied in the treatment of sialorrhea associated with Parkinson's Disease, parkinsonian syndromes, cerebral palsy, head and neck carcinoma, neurodegenerative disease, stroke, and amytrophic lateral sclerosis (ALS).[22-24] Data with Dysport come from two small controlled trials.[22,23] AAN guidelines state that botulinum toxin is probably safe and effective and should be considered (Level B).[16]
- **Spasticity, Other Than Lower and Upper Limb (i.e., spasticity or hypertonia due to cerebral palsy, stroke, brain injury, spinal cord injury, multiple sclerosis, hemifacial spasm):** Oral medications have a long history in spasticity treatment (e.g., baclofen, benzodiazepines, tizanidine, dantrolene, phenytoin, or gabapentin) yet they have dose-limiting side effects and limited diffusion across the blood brain barrier.[25] Several randomized, controlled trials have evaluated the efficacy of Dysport in spasticity of various etiologies in both upper and lower limbs.[11,25-27] Other randomized, controlled trials evaluated botulinum toxin A for the management of upper limb spasticity in children with cerebral palsy and showed significant improvement in spasticity/tone, range of motion, and functional gains after botulinum toxin A injections.[28] Treatment with botulinum toxin A in hemifacial spasm appears to remain effective over long-term use of several years (4 to 10 years); most cases do not require a dosage increase.[29] In an observational study, patients (n = 133) with hemifacial spasm and reinnervation synkinesias were exclusively treated with either Dysport or Botox for 6 years; Botox and Dysport were similarly effective and the therapeutic effect was stable throughout the observation period.[30]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Dysport. Use should be limited to the treatment of medical conditions. Prescription benefit coverage of this product is not recommended for cosmetic conditions. All approvals are provided for 1 year.

Automation: None

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indications

10. **Cervical Dystonia (spasmodic torticollis).** Approve for 1 year.
    (Note: Cervical dystonia is also known as spasmodic or cervical torticollis.)

11. **Spasticity, Lower Limb**. Approve for 1 year.
    (Note: For other forms of spasticity that do not fit this condition of approval, see Other Uses with Supportive Evidence, Spasticity.)

12. **Spasticity, Upper Limb.** Approve for 1 year.
    (Note: For other forms of spasticity that do not fit this condition for coverage, see Other Uses with Supportive Evidence, Spasticity.)

Other Uses with Supportive Evidence

13. **Anal Fissure (anal sphincter).** Approve for 1 year.

14. **Blepharospasm.** Approve for 1 year.

15. **Frey's Syndrome (gustatory sweating).** Approve for 1 year.

16. **Hyperhidrosis, Primary Axillary.** Approve for 1 year if the patient has tried at least one topical agent (e.g., topical aluminum chloride, Qbrexza™ [glycopyrronium cloth 2.4% for topical use]).

17. **Sialorrhea, Chronic.** Approve for 1 year.

18. **Spasticity, Other Than Lower and Upper Limb (i.e., spasticity or hypertonia due to cerebral palsy, stroke, brain injury, spinal cord injury, multiple sclerosis, hemifacial spasm).** Approve for 1 year.
    (Note: For lower limb spasticity and upper limb spasticity, see FDA-Approved Indication criteria #2 and #3 [above].)

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Dysport has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

6. **Cosmetic Uses** (e.g., facial rhytides, frown lines, glabellar wrinkling, horizontal neck rhytides, mid and lower face and neck rejuvenation, platsymal bands, rejuvenation of the periorbital region). Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical pharmacy benefit.

7. **Fibromyalgia.** Limited data are available with Botox. No data are available with Dysport at this time.

8. **Ophthalmic Disorders, Other Than Blepharospasm (e.g., esotropia, exotropia, nystagmus, facial nerve paresis).** More data are needed to define the place of therapy of Dysport in the treatment of ophthalmic disorders. Botulinum toxin A has been successful in improving or treating many ophthalmic disorders. Retrospective reviews conclude that botulinum toxin A may have a role in the treatment of exotropia.[31,32] Dysport improved visual acuity in patients with acquired symptomatic nystagmus from multiple sclerosis or brain-stem hemorrhage in one case series (n = 12).[33] Data from an uncontrolled study have shown Dysport to be beneficial in the treatment of fourth nerve palsy.[34]

9. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual review	No change to criteria.	03/08/2017
Annual revision	Removal of Allergic rhinitis, Bladder/voiding/urethral dysfunction, Crocodile tears syndrome, Essential tremor, Gait freezing in Parkinson's disease, and Vaginismus from Conditions Not Recommended for Approval.	04/11/2018
Annual revision	**Hyperhidrosis, Primary Axillary:** Qbrexza (glycopyrronium cloth) added to list of medications that satisfy requirement for trial of a topical agent. **Spasticity, Other Than Lower and Upper Limb:** "Other than lower and upper limb" added to clarify this covers uses other than the FDA-approved indications. **Ophthalmic Disorders, Other Than Blepharospasm (e.g., esotropia, exotropia, nystagmus, facial nerve paresis):** The phrase "other than blepharospasm" was added for clarification, and "i.e." was changed to "e.g.".	05/08/2019
Annual revision	**FDA-Approved Indications:** • "Cervical Dystonia (torticollis)" updated to "Cervical Dystonia (spasmodic torticollis)". **Other Uses with Supportive Evidence:** • "Salivary Hypersecretion" updated to "Sialorrhea, Chronic."	06/03/2020

PRIOR AUTHORIZATION POLICY

POLICY: Botulinum Toxins – Myobloc® (rimabotulinumtoxinB injection – Solstice Neurosciences)

DATE REVIEWED: 06/03/2020

OVERVIEW

Myobloc® (rimabotulinumtoxinB) is indicated for the treatment of patients with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia.[1] It is also indicated for the treatment of chronic sialorrhea. There are published studies and case reports supporting the use of botulinum toxin type B for other medical conditions.

Like the botulinum toxin type A products (Botox® and Botox® Cosmetic [onabotulinumtoxinA], Dysport® [abobotulinumtoxinA]), and Xeomin® [incobotulinumtoxinA]), Myobloc has also been used to treat cosmetic conditions such as glabellar rhytides, crow's feet, and platysmal bands, and it has been used in brow lifts.

Albeit rare, repeated injections of botulinum toxin type A products can lead to the formation of neutralizing antibodies which can result in clinical resistance. It is important to note that the presence of botulinum toxin type A antibodies are not equivalent to clinical nonresponse. Myobloc is antigenically distinct from botulinum toxin type A and, therefore, in some cases may be used as an alternative to botulinum toxin type A in type A-resistant patients.[2] Studies have attempted to establish a conversion ratio between botulinum toxin products, with variable results. In general, conversion ratios of 1:1 for Botox to Xeomin, 1:3 for Botox to Dysport, and 1:50 to 1:100 for Botox to Myobloc have been suggested.[3,4]

Other Uses with Supportive Evidence

Botulinum toxins, including Myobloc, have been studied in a variety of indications outside of FDA-approved uses. Literature is available to support use of Myobloc in the following conditions:

- **Bladder Dysfunction:** Botulinum toxin type B was shown to be effective in improving symptoms of overactive bladder in one small randomized, double-blind, placebo-controlled study (formulation not specified) in patients unresponsive to oral antimuscarinic agents.[5] Oral pharmacologic therapy with antimuscarinic agents is the mainstay of drug therapy in the treatment of overactive bladder.[6,7,]
- **Hyperhidrosis, Palmar or Primary Axillary:** Myobloc was shown to be effective in treating palmar hyperhidrosis in one small, randomized, double-blind, placebo-controlled study and a second prospective, open, single-blind, multicenter study.[8,9,] Botulinum toxin type B was shown to be effective in treating axillary hyperhidrosis in one randomized, double-blind, placebo-controlled trial (using Myobloc) and one small, open-label study (using Neurobloc).[10,11,] There was no significant difference between Botox and Myobloc/Neurobloc in duration of effect in one small comparative study in patients with axillary hyperhidrosis.[12] In a small (n = 10), single-blind, comparative study, botulinum toxin type B (Neurobloc) was significantly more effective than Botox in decreasing sweat weight and area.[13] Topical antiperspirants (e.g., topical aluminum chloride) are recommended first-line therapies for the treatment of primary hyperhidrosis.[14-16,] In the setting of primary axillary hyperhidrosis, Qbrexza, a topical anticholinergic, may also be used first-line.[17] The AAN notes that botulinum toxin therapy is established safe and effective in axillary hyperhidrosis (Level A).[18] AAN guidelines state that botulinum toxins are probably safe and effective and should be considered for palmar hyperhidrosis (Level B).
- **Myofascial Pain:** Myobloc was effective in reducing myofascial pain associated with piriformis syndrome in a small open-label study; 95% of patients reported fair to excellent improvement in pain.[19]
- **Spasticity (i.e., spasticity or hypertonia due to cerebral palsy, stroke, brain injury, spinal cord injury, multiple sclerosis, hemifacial spasm):** Botulinum toxin type B was shown to be effective in reducing spasticity in one open-label study (formulation not specified) in children with spastic or dystonic movement disorders[20] and in a randomized, double-blind, placebo-controlled study (n = 24) in hemiparetic patients with disabling elbow flexor overactivity after stroke or traumatic brain injury.[21] In one small, randomized, double-blind, placebo-controlled study in patients with upper-limb post-stroke spasticity (n = 15), Myobloc reduced spasticity at 2 weeks but was not statistically

significant at other follow-up visits.[22] Botulinum toxin type B was shown to be effective in treating hemifacial spasm in one small open-label study (formulation not specified).[23] Per American Academy of Neurology (AAN) guidelines, botulinum toxin is possibly effective and may be considered for hemifacial spasm (Level C).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Myobloc. Use should be limited to the treatment of medical conditions. Prescription benefit coverage of this product is not recommended for cosmetic conditions. All approvals are provided for 1 year.

Automation: None

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Myobloc is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Cervical Dystonia (spasmodic torticollis).** Approve for 1 year.

2. **Sialorrhea, Chronic.** Approve for 1 year.

Other Uses with Supportive Evidence

3. **Bladder Dysfunction.** Approve for 1 year in patients who meet the following conditions (A and B):
   - **A)** Patient has tried at least one other pharmacologic therapy (e.g., oral antimuscarinic agents [for example: oxybutynin, tolterodine tartrate, trospium chloride, Enablex, Toviaz, Vesicare]), AND
   - **B)** Myobloc is being prescribed by or after consultation with a urologist.

4. **Hyperhidrosis, Palmar or Primary Axillary.** Approve for 1 year in patients who meet the following conditions (A and B):
   - **A)** Patient has tried at least one topical agent (e.g., topical aluminum chloride, Qbrexza™ [glycopyrronium cloth 2.4% for topical use]); AND
   - **B)** Patient has tried Botox.

5. **Myofascial Pain.** Approve for 1 year.

6. **Spasticity (i.e., spasticity or hypertonia due to cerebral palsy, stroke, brain injury, spinal cord injury, multiple sclerosis, hemifacial spasm).** Approve for 1 year.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Myobloc has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Cosmetic Uses (e.g., facial and/or glabellar rhytides [wrinkles, lines], crow's feet, brow lifts, platysmal bands).** Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical pharmacy benefit.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed

Selected revision	Migraine prophylaxis: Updated criteria to include trial of triptans or contraindication to triptans.	08/01/2018
Selected revision	Migraine prophylaxis: Change to require verification of specific therapies that have been tried for migraine prophylaxis.	09/19/2018
Annual revision	**Hyperhidrosis, Palmar or Primary Axillary:** Qbrexza was added as an example of a medication that satisfies the requirement for trial of a topical product.	05/08/2019
Selected revision	**Sialorrhea (Salivary Hypersecretion), Chronic:** Moved to FDA-approved indications. "Chronic" added for clarification and to align with product labeling.	09/04/2019
Annual revision	**FDA-Approved Indications:** • "Sialorrhea (Salivary Hypersecretion), Chronic" updated to "Sialorrhea, Chronic." **Other Uses with Supportive Evidence:** • "Anal Fissures" removed from policy. • "Blepharospasm" removed from policy. • "Hemifacial spasm" rolled into approval condition of "Spasticity". • "Migraine headache prophylaxis in patients with chronic migraine" removed from policy. • "Speech/Voice Disorder" removed from policy.	06/03/2020

PRIOR AUTHORIZATION POLICY

POLICY: Botulinum Toxins – Xeomin® (incobotulinumtoxinA for injection – Merz)

DATE REVIEWED: 06/03/2020

OVERVIEW

Xeomin® (incobotulinumtoxinA) is indicated in adult patients for the following:

- blepharospasm;
- cervical dystonia;
- chronic sialorrhea; AND
- upper limb spasticity.[1]

Xeomin is also indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugators and/or procerus muscle activity in adult patients.

The labels for the botulinum toxin type A products (Botox® [onabotulinumtoxinA], Dysport® [abobotulinumtoxinA], and Xeomin) state that there is a lack of interchangeability between the products for various reasons, including differences in the units of biological activity.[1-3] However, studies have demonstrated that identical units of Xeomin and Botox were equally effective.[4-7] Based on published literature, it has been established that Xeomin and Botox have identical therapeutic effects and adverse event (AE) profiles with a 1:1 conversion ratio.[7]

Other Uses with Supportive Evidence

Botulinum toxins, including Xeomin, have been studied in a variety of indications outside of FDA-approved uses. Literature is available to support use of Xeomin in the following conditions:

- **Hyperhidrosis, Primary Axillary, Palmar/Plantar, and Facial:** Overall, topical antiperspirants (e.g., aluminum chloride) are the recommended first-line therapy for the treatment of primary axillary hyperhidrosis and focal hyperhidrosis.[8-11] In the setting of primary axillary hyperhidrosis, Qbrexza, a topical anticholinergic, may also be used first-line.[12] The efficacy of Xeomin in the treatment of palmar/plantar hyperhidrosis and cranial hyperhidrosis was demonstrated in patients (n = 20) previously treated with Botox.[13] In a double-blind clinical trial, patients (n = 25) with moderate or severe palmar hyperhidrosis received in the same session intradermal injections of Botox on one hand and Xeomin on the other; the two products appeared to be comparable.[14] The

efficacy of Xeomin for axillary hyperhidrosis was demonstrated in a prospective, double-blind, head-to-head intra-individual comparison trial vs. Botox.[15] A total of 46 patients received 50 units of botulinum toxin type A treatment (Xeomin in one axilla, and Botox in the other axilla). Efficacy and tolerability were similar between Botox and Xeomin. In addition, the efficacy of Xeomin in the treatment of axillary hyperhidrosis was demonstrated in patients (n = 41) previously treated with Botox.[13] AAN guidelines state that botulinum toxins are probably safe and effective and should be considered for palmar hyperhidrosis (plantar and facial hyperhidrosis are not addressed in the AAN guideline).[16]

- **Spasticity, Other Than Upper Limb (i.e., spasticity or hypertonia due to cerebral palsy, stroke, brain injury, spinal cord injury, multiple sclerosis, hemifacial spasm):** Oral medications have a long history in spasticity treatment (e.g., baclofen, benzodiazepines, phenytoin, or gabapentin) yet they have dose-limiting side effects and limited diffusion across the blood brain barrier.[17] In a prospective, randomized study in patients (n = 192) with upper limb spasticity due to stroke, brain injury, multiple sclerosis, or cerebral palsy, the majority of Xeomin-treated patients had improvement in functional disability and in muscle tone.[18] In a Phase III randomized study in patients (n = 148) with post-stroke upper limb spasticity, Xeomin was significantly more effective than placebo at Week 4 and at Week 12.[19] In addition, the efficacy of Xeomin in the treatment of hemispasticity, arm spasticity, generalized spasticity, paraspasticity, leg spasticity, and hemifacial spasm was demonstrated in patients (n = 95) previously treated with Botox for at least 1 year under stable conditions and crossed over in a blinded fashion to Xeomin for 3 years.[13] Per the AAN, botulinum toxin is established effective in upper and lower limb spasticity and in cerebral palsy (Level A), and it may be considered in hemifacial spasm (Level C).[20,21]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Xeomin. Use should be limited to the treatment of medical conditions. Prescription benefit coverage of this product is not recommended for cosmetic conditions. All approvals are provided for 1 year.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indications

19. **Blepharospasm**. Approve for 1 year.

20. **Cervical Dystonia (spasmodic torticollis).** Approve for 1 year.
(Note: Cervical dystonia is also known as spasmodic or cervical torticollis.)

21. **Sialorrhea, Chronic.** Approve for 1 year.

22. **Spasticity, Upper Limb.** Approve for 1 year.
(Note: For other forms of spasticity that do not fit this condition of approval, see Other Uses with Supportive Evidence, Spasticity.)

Other Uses with Supportive Evidence

23. **Hyperhidrosis – Primary Axillary, Palmar/Plantar, and Facial.** Approve for 1 year if the patient has tried at least one topical agent (e.g., aluminum chloride, Qbrexza™ [glycopyrronium cloth 2.4% for topical use]).

24. **Spasticity, Other Than Upper Limb (i.e., spasticity or hypertonia due to cerebral palsy, stroke, brain injury, spinal cord injury, multiple sclerosis, hemifacial spasm).** Approve for 1 year. (Note: For upper limb spasticity, see FDA-Approved Indication criterion #4 [above].)

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Xeomin has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

10. **Cosmetic Uses** (e.g., facial rhytides, frown lines, glabellar wrinkling, horizontal neck rhytides, mid and lower face and neck rejuvenation, platsymal bands, rejuvenation of the periorbital region). Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical pharmacy benefit.

11. **Fibromyalgia.** Limited data are available with Botox. No data are available with Xeomin at this time.

12. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual revision	Combined Primary Axillary Hyperhidrosis, Palmar/Plantar Hyperhidrosis and Facial Hyperhidrosis under one Other Use with Supportive Evidence; previously they were listed separately. Removal of Allergic rhinitis, Crocodile tears syndrome, Dysphagia, Gait freezing, Interstitial cystitis, Trigeminal neuralgia, and Vaginismus from Conditions Not Recommended for Approval.	04/11/2018
Selected revision	Moved criterion for Chronic Sialorrhea (Salivary Hypersecretion) to FDA-Approved Indications from Other Uses with Supportive Evidence.	7/18/2018
Annual revision	**Hyperhidrosis – Primary Axillary, Palmar/Plantar, and Facial:** Added Qbrexza to list of medications that satisfy requirement for trial of a topical agent. **Spasticity, Other Than Upper Limb:** "Other than upper limb" added to clarify this covers uses other than the FDA-approved indications.	05/08/2019
Selected revision	**Blepharospasm:** Removed requirement for previous trial of Botox.	05/22/2019
Annual revision	**FDA-Approved Indications:** • "Cervical Dystonia" updated to "Cervical Dystonia (spasmodic torticollis)". • "Sialorrhea (Salivary Hypersecretion), Chronic" updated to "Sialorrhea, Chronic."	06/03/2020

PRIOR AUTHORIZATION POLICY

POLICY: Calcitonin Gene-Related Peptide Inhibitors – Aimovig® (erenumab injection for subcutaneous use – Amgen)

DATE REVIEWED: 04/15/2020

OVERVIEW

Aimovig, a calcitonin gene-related peptide (CGRP) receptor antagonist, is indicated for the preventive treatment of migraine in adults.[1] Aimovig is a human monoclonal antibody that binds to the CGRP receptor and antagonizes CGRP receptor function. The recommended dosage of Aimovig is 70 mg injected subcutaneously (SC) once monthly. Some patients may benefit from a dosage of 140 mg SC once monthly.

Disease Overview

Migraine is a common, chronic condition marked by paroxysmal, unilateral attacks of moderate-to-severe throbbing headache which is aggravated by routine physical activity (e.g., walking or climbing stairs) and associated with nausea, vomiting, and/or photophobia and phonophobia.[2] Migraine headache episodes typically last 4 to 72 hours if untreated. Migraine affects approximately 15% of US adults.[3] Migraines have been defined as chronic or episodic. Chronic migraine is described by the International Headache Society as headache occurring on ≥ 15 days/month for > 3 months and has the features of migraine headache on ≥ 8 days/month.[2] Episodic migraine is characterized by headaches that occur < 15 days/month.[4] Patients with episodic migraine may transform to chronic migraine over time at a rate of about 2.5% of episodic-migraine patients/year. Potential strategies for preventing migraine transformation include preventing and treating headaches, lifestyle modifications, or effective management of comorbidities (e.g., obesity, obstructive sleep apnea, depression, anxiety). Episodic migraine is more common than chronic migraine; however, chronic migraine is associated with a markedly greater personal and societal burden.

Guidelines

An updated assessment of the **preventive and acute treatment of migraine** by the **American Headache Society** (2018) reaffirms previous migraine guidelines.[5] Patients with migraine should be considered for preventive treatment when attacks significantly interfere with patients' daily routines despite acute treatment; frequent attacks (≥ 4 monthly headache days); contraindication to, failure, overuse, or adverse events with acute treatments; or patient preference. Before developing a preventive treatment plan, the appropriate use (e.g., drug type, route and timing of administration, frequency) of acute treatments should be initiated and coupled with education and lifestyle modifications. All patients with migraine should be offered a trial of acute treatment. Based on the level of evidence for efficacy and the American Academy of Neurology (AAN) scheme for classification of evidence, the following oral treatments have established efficacy and should be offered for migraine prevention: antiepileptic drugs (divalproex sodium, valproate sodium, topiramate [not for women of childbearing potential without a reliable method of birth control]); beta-blockers (metoprolol, propranolol, timolol); and frovatriptan (for short-term preventive treatment of menstrual migraine).[6] The following treatments are probably effective and should be considered for migraine prevention: antidepressants (amitriptyline, venlafaxine); beta-blockers (atenolol, nadolol); and angiotensin receptor blockers (candesartan).

Four injectable preventive therapies for migraine are mentioned in the AHS consensus statement: Botox® (onabotulinumtoxinA injection) and three monoclonal antibodies targeting CGRP (Aimovig, Ajovy® [fremanezumab-vfrm injection], and Emgality® [galcanezumab-gnlm injection]).[5] The update notes that a CGRP inhibitor should only be initiated in patients who are diagnosed with migraine, have ≥ 4 migraine headache days per month, and have intolerance or inadequate response to 6-week trials of at least two traditional oral migraine preventive medications. Additional criteria apply depending on the number and severity of monthly headache days. Clinical judgment may result in an emerging treatment being added to one or more established treatments. If initiating treatment with a CGRP inhibitor in a patient already on a preventive treatment, it is appropriate to add the CGRP inhibitor to the existing regimen and make no other changes until the effectiveness of the CGRP inhibitor is determined since the risk of interactions between traditional oral migraine preventive medications and the CGRP inhibitors is minimal or nonexistent. Making a decision regarding continuation of therapy for a CGRP inhibitor requires a trial of the medication for at least 3 months, and treatment should be continued only if benefits can be documented during that time (e.g., reduction in mean monthly headache days of ≥ 50% relative to the pretreatment baseline). Since migraine may improve or remit over time, it is important to reevaluate therapeutic response and, if possible, taper or discontinue treatment if patients no longer meet the criteria for offering preventive treatment. However, once control is established, the decision to discontinue or taper treatment should be a shared decision between patient and clinician.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Aimovig. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Aimovig is recommended in those who meet the following criteria:

FDA-Approved Indications

9. Migraine Headache Prevention. Approve Aimovig for 1 year if the patient meets the following criteria (A, B, C, and D):

- **2.** Patient is ≥ 18 years of age; AND
- **3.** Patient has ≥ 4 migraine headache days per month (prior to initiating a migraine-preventative medication); AND
- **4.** Patient has tried at least two standard prophylactic pharmacologic therapies, each from a different pharmacologic class (e.g., angiotensin receptor blocker, angiotensin converting enzyme inhibitor, anticonvulsant, β-blocker, calcium channel blocker, tricyclic antidepressant, other antidepressant), and meets ONE of the following criteria (i, ii, or iii):
  - **i.** The patient has had inadequate efficacy to both of those standard prophylactic pharmacologic therapies, according to the prescriber; OR
  - **ii.** The patient has experienced adverse event(s) severe enough to warrant discontinuation of both of those standard prophylactic pharmacologic therapies, according to the prescriber; OR
  - **iii.** The patient has had inadequate efficacy to one standard prophylactic pharmacologic therapy and has experienced adverse event(s) severe enough to warrant discontinuation to another standard prophylactic pharmacologic therapy, according to the prescriber; AND
- **5.** Patient meets ONE of the following (i or ii):
  - **i.** Patient has tried at least one triptan therapy; OR
  - **ii.** Patient has a contraindication to triptan(s) according to the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Aimovig has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Acute Treatment of Migraine. Aimovig has not been studied for the acute treatment of migraine.

2. Cluster Headache, Treatment or Prevention. Aimovig has not been studied in patients with cluster headache. The pivotal trials of Aimovig excluded patients with this condition.[7,8]

3. Combination Therapy with Ajovy® (fremanezumab-vfrm injection for subcutaneous use), Emgality® (galcanezumab-gnlm injection for subcutaneous use), or Vyepti™ (eptinezumab-jjmr injection for intravenous use). Aimovig, Ajovy, Emgality, and Vyepti are calcitonin gene-related peptide (CGRP) inhibitors for migraine prevention and have not been studied for use in combination with another agent in the same class.[9-11]

4. **Hemiplegic Migraine, Treatment or Prevention.** Aimovig has not been studied in patients with hemiplegic migraine. The pivotal trials of Aimovig excluded patients with this condition.[7,8]

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	05/18/2018
Selected revision	The criterion requiring inadequate responses at least two standard prophylactic pharmacologic therapies from two different pharmacologic classes was modified to clarify that the patient had inadequate efficacy or serious adverse events to those preventive therapies.	06/13/2018
Selected revision	Changed the document name to Calcitonin Gene-Related Peptide (CGRP) Inhibitors – Aimovig PA to take into account the different mechanism of action of the new CGRP inhibitor Ajovy. Added a new Condition Not Recommended for Approval for combination therapy with Ajovy or Emgality.	10/03/2018
Annual revision	No change to criteria.	05/29/2019
Annual revision	Throughout the criteria, "prescribing physician" was changed to "prescriber". For the Condition Not Recommended for Approval of combination therapy, Vyepti was added to the list of injectable calcitonin gene-related peptide inhibitors. For the Conditions Not Recommended for Approval of cluster headache and hemiplegic migraine, "treatment or prevention" was added to clarify the intent.	04/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Calcitonin Gene-Related Peptide Inhibitors – Ajovy® (fremanezumab-vfrm injection for subcutaneous use – Teva)

DATE REVIEWED: 04/15/2020

OVERVIEW

Ajovy, a calcitonin gene-related peptide (CGRP) antagonist, is indicated for the preventive treatment of migraine in adults.[1] Ajovy is a human monoclonal antibody that binds to the CGRP ligand and blocks its binding to the receptor. The recommended dosage of Ajovy is 225 mg injected subcutaneously (SC) once monthly or 675 mg every 3 months (quarterly), which is administered as three consecutive SC injections of 225 mg each. A healthcare professional, patient, and/or caregiver may administer Ajovy.

Disease Overview

Migraine is a common, chronic condition marked by paroxysmal, unilateral attacks of moderate-to-severe throbbing headache which is aggravated by routine physical activity (e.g., walking or climbing stairs) and associated with nausea, vomiting, and/or photophobia and phonophobia.[2] Migraine headache episodes typically last 4 to 72 hours if untreated. Migraine affects approximately 15% of US adults.[3] Migraines have been defined as chronic or episodic. Chronic migraine is described by the International Headache Society as headache occurring on ≥ 15 days/month for > 3 months and has the features of migraine headache on ≥ 8 days/month.[2] Episodic migraine is characterized by headaches that occur < 15 days/month.[4] Patients with episodic migraine may transform to chronic migraine over time at a rate of about 2.5% of episodic-migraine patients/year. Potential strategies for preventing migraine transformation include preventing and treating headaches, lifestyle modifications, or effective management of comorbidities (e.g., obesity, obstructive sleep apnea, depression, anxiety). Episodic migraine is more common than chronic migraine; however, chronic migraine is associated with a markedly greater personal and societal burden.

Guidelines

An updated assessment of the **preventive and acute treatment of migraine** by the **American Headache Society** (2018) reaffirms previous migraine guidelines.[5] Patients with migraine should be considered for preventive treatment when attacks significantly interfere with patients' daily routines despite acute treatment; frequent attacks (≥ 4 monthly headache days); contraindication to, failure, overuse, or adverse events with acute treatments; or patient preference. Before developing a preventive treatment plan, the appropriate use (e.g., drug type, route and timing of administration, frequency) of acute treatments should be initiated and coupled with education and lifestyle modifications. All patients with migraine should be offered a trial of acute treatment. Based on the level of evidence for efficacy and the American Academy of Neurology (AAN) scheme for classification of evidence, the following oral treatments have established efficacy and should be offered for migraine prevention: antiepileptic drugs (divalproex sodium, valproate sodium, topiramate [not for women of childbearing potential without a reliable method of birth control]); beta-blockers (metoprolol, propranolol, timolol); and frovatriptan (for short-term preventive treatment of menstrual migraine).[6] The following treatments are probably effective and should be considered for migraine prevention: antidepressants (amitriptyline, venlafaxine); beta-blockers (atenolol, nadolol); and angiotensin receptor blockers (candesartan).

Four injectable preventive therapies for migraine are mentioned in the AHS consensus statement: Botox® (onabotulinumtoxinA injection) and three monoclonal antibodies targeting CGRP (Aimovig, Ajovy® [fremanezumab-vfrm injection], and Emgality® [galcanezumab-gnlm injection]).[5] The update notes that a CGRP inhibitor should only be initiated in patients who are diagnosed with migraine, have ≥ 4 migraine headache days per month, and have intolerance or inadequate response to 6-week trials of at least two traditional oral migraine preventive medications. Additional criteria apply depending on the number and severity of monthly headache days. Clinical judgment may result in an emerging treatment being added to one or more established treatments. If initiating treatment with a CGRP inhibitor in a patient already on a preventive treatment, it is appropriate to add the CGRP inhibitor to the existing regimen and make no other changes until the effectiveness of the CGRP inhibitor is determined since the risk of interactions between

traditional oral migraine preventive medications and the CGRP inhibitors is minimal or nonexistent. Making a decision regarding continuation of therapy for a CGRP inhibitor requires a trial of the medication for at least 3 months, and treatment should be continued only if benefits can be documented during that time (e.g., reduction in mean monthly headache days of ≥ 50% relative to the pretreatment baseline). Since migraine may improve or remit over time, it is important to reevaluate therapeutic response and, if possible, taper or discontinue treatment if patients no longer meet the criteria for offering preventive treatment. However, once control is established, the decision to discontinue or taper treatment should be a shared decision between patient and clinician.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Ajovy. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ajovy is recommended in those who meet the following criteria:

FDA-Approved Indications

10. Migraine Headache Prevention. Approve Ajovy for 1 year if the patient meets the following criteria (A, B, C, and D):

- **6.** Patient is ≥ 18 years of age; AND
- **7.** Patient has ≥ 4 migraine headache days per month (prior to initiating a migraine-preventative medication); AND
- **8.** Patient has tried at least two standard prophylactic pharmacologic therapies, each from a different pharmacologic class (e.g., angiotensin receptor blocker, angiotensin converting enzyme inhibitor, anticonvulsant, β-blocker, calcium channel blocker, tricyclic antidepressant, other antidepressant), and meets ONE of the following criteria (i, ii, or iii):
  - **i.** The patient has had inadequate efficacy to both of those standard prophylactic pharmacologic therapies, according to the prescriber; OR
  - **ii.** The patient has experienced adverse event(s) severe enough to warrant discontinuation of both of those standard prophylactic pharmacologic therapies, according to the prescriber; OR
  - **iii.** The patient has had inadequate efficacy to one standard prophylactic pharmacologic therapy and has experienced adverse event(s) severe enough to warrant discontinuation to another standard prophylactic pharmacologic therapy, according to the prescriber; AND
- **9.** Patient meets ONE of the following (i or ii):
  - **i.** Patient has tried at least one triptan therapy; OR
  - **ii.** Patient has a contraindication to triptan(s) according to the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Ajovy has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

6. Acute Treatment of Migraine. Ajovy has not been studied for the acute treatment of migraine.

7. **Cluster Headache, Treatment or Prevention.** Ajovy has not been found to be effective in in patients with chronic or episodic cluster headache.[7]

8. **Combination Therapy with Aimovig™ (erenumab-aooe injection for subcutaneous use), Emgality™ (galcanezumab-gnlm injection for subcutaneous use), or Vyepti™ (eptinezumab-jjmr injection for intravenous use).** Ajovy, Aimovig, Emgality, and Vyepti are calcitonin gene-related peptide (CGRP) antagonists for migraine prevention and have not been studied for use in combination with another agent in the same class.[8-10]

9. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	09/19/2018
Selected revision	Changed the document name to Calcitonin Gene-Related Peptide (CGRP) Inhibitors – Ajovy PA to take into account the different mechanisms of action of the CGRP inhibitors. Added Emgality to the Condition Not Recommended for Approval for combination therapy with Aimovig.	10/03/2018
Annual revision	No change to criteria.	05/29/2019
Annual revision	Throughout the criteria, "prescribing physician" was changed to "prescriber". For the Condition Not Recommended for Approval of combination therapy, Vyepti was added to the list of injectable calcitonin gene-related peptide inhibitors. For the Condition Not Recommended for Approval of cluster headache, "treatment or prevention" was added to clarify the intent.	04/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Calcitonin Gene-Related Peptide Inhibitors – Emgality® (galcanezumab-gnlm injection for subcutaneous use – Lilly)

DATE REVIEWED: 04/15/2020

OVERVIEW

Emgality, a calcitonin gene-related peptide (CGRP) antagonist, is indicated for the preventive treatment of migraine in adults and for the treatment of episodic cluster headache in adults.[1] Emgality is a human monoclonal antibody that binds to the CGRP ligand and blocks its binding to the receptor. The recommended dosage of Emgality for the prevention of migraine is 240 mg (two consecutive subcutaneous [SC] injections of 120 mg each) once as a loading dose, followed by monthly doses of 120 mg injected subcutaneously. For cluster headache, Emgality is dosed as 300 mg SC (administered as three consecutive injections of 100 mg each) at the onset of the cluster period, and then monthly until the end of the cluster period. Emgality is intended for patient self-administration.

Disease Overview

Migraine is a common, chronic condition marked by paroxysmal, unilateral attacks of moderate-to-severe throbbing headache which is aggravated by routine physical activity (e.g., walking or climbing stairs) and associated with nausea, vomiting, and/or photophobia and phonophobia.[2] Migraine headache episodes typically last 4 to 72 hours if untreated. Migraine affects approximately 15% of US adults.[3] Migraines have been defined as chronic or episodic. Chronic migraine is described by the International Headache Society as headache occurring on ≥ 15 days/month for > 3 months and has the features of migraine headache on ≥ 8 days/month.[2] Episodic migraine is characterized by headaches that occur < 15 days/month.[4] Patients with episodic migraine may transform to chronic migraine over time at a rate of about 2.5% of episodic-migraine patients/year. Potential strategies for preventing migraine transformation include preventing and treating headaches, lifestyle modifications, or effective management of comorbidities (e.g., obesity, obstructive sleep apnea, depression, anxiety). Episodic migraine is more common than chronic migraine; however, chronic migraine is associated with a markedly greater personal and societal burden.

Cluster headache is the most common of the group of headache disorders known as the trigeminal autonomic cephalalgias, with a lifetime prevalence exceeding 1 in 1,000.[5] Cluster headaches are associated with attacks of severe, strictly unilateral pain which is orbital, supraorbital, temporal, or in any combination of these sites, lasting 15 to 180 minutes.[2] The headaches occur from once every other day to eight times a day. Cluster headache is considered among the most severe of the primary headache disorders because of extreme pain, associated autonomic symptoms, and high attack frequency.[5] In addition, a large proportion of patients with cluster headache have chronic cluster headache, which features only brief or no remission periods, and may be particularly refractory to medical therapies. Patients with cluster headache are often suboptimally treated, even though treatment of cluster headache in accordance with guidelines is associated with better outcomes.

Guidelines

An updated assessment of the **preventive and acute treatment of migraine** by the **American Headache Society** (2018) reaffirms previous migraine guidelines.[6] Patients with migraine should be considered for preventive treatment when attacks significantly interfere with patients' daily routines despite acute treatment; frequent attacks (≥ 4 monthly headache days); contraindication to, failure, overuse, or adverse events with acute treatments; or patient preference. Before developing a preventive treatment plan, the appropriate use (e.g., drug type, route and timing of administration, frequency) of acute treatments should be initiated and coupled with education and lifestyle modifications. All patients with migraine should be offered a trial of acute treatment. Based on the level of evidence for efficacy and the American Academy of Neurology (AAN) scheme for classification of evidence, the following oral treatments have established efficacy and should be offered for migraine prevention: antiepileptic drugs (divalproex sodium, valproate sodium, topiramate [not for women of childbearing potential without a reliable method of birth control]); beta-blockers (metoprolol, propranolol, timolol); and frovatriptan (for short-term preventive treatment of menstrual migraine).[7] The following treatments are probably effective and should be considered for migraine prevention: antidepressants (amitriptyline, venlafaxine); beta-blockers (atenolol, nadolol); and angiotensin receptor blockers (candesartan).

Four injectable preventive therapies for migraine are mentioned in the AHS consensus statement: Botox® (onabotulinumtoxinA injection) and three monoclonal antibodies targeting CGRP (Aimovig, Ajovy® [fremanezumab-vfrm injection], and Emgality® [galcanezumab-gnlm injection]).[6] The update notes that a CGRP inhibitor should only be initiated in patients who are diagnosed with migraine, have ≥ 4 migraine headache days per month, and have intolerance or inadequate response to 6-week trials of at least two traditional oral migraine preventive medications. Additional criteria apply depending on the number and severity of monthly headache days. Clinical judgment may result in an emerging treatment being added to one or more established treatments. If initiating treatment with a CGRP inhibitor in a patient already on a preventive treatment, it is appropriate to add the CGRP inhibitor to the existing regimen and make no other changes until the effectiveness of the CGRP inhibitor is determined since the risk of interactions between traditional oral migraine preventive medications and the CGRP inhibitors is minimal or nonexistent. Making a decision regarding continuation of therapy for a CGRP inhibitor requires a trial of the medication for at least 3 months, and treatment should be continued only if benefits can be documented during that time (e.g., reduction in mean monthly headache days of ≥ 50% relative to the pretreatment baseline). Since migraine may improve or remit over time, it is important to reevaluate therapeutic response and, if possible, taper or discontinue treatment if patients no longer meet the criteria for offering preventive treatment. However, once control is established, the decision to discontinue or taper treatment should be a shared decision between patient and clinician.

The **American Headache Society** has published evidence-based guidelines on the **treatment of cluster headache** (2016).[5] The guidelines recommend sumatriptan subcutaneous, zolmitriptan nasal spray, and high flow oxygen for acute treatment. For prophylactic therapy, suboccipital steroid injection has been established as effective for the prophylactic therapy of episodic and chronic cluster headache (Level A). Lithium, verapamil, and melatonin are considered possibly effective for the prophylactic therapy of episodic and chronic cluster headache (Level C). Currently, there is insufficient evidence to make a recommendation for frovatriptan and prednisone (Level U).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Emgality. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Emgality is recommended in those who meet the following criteria:

FDA-Approved Indications

11. Episodic Cluster Headache Treatment. Approve Emgality for 6 months if the patient meets the following criteria (A, B, C, and D):
- **10.** Patient is ≥ 18 years of age; AND
- **11.** Patient has between one headache every other day and eight headaches per day; AND
- **12.** Patient has tried at least one standard prophylactic pharmacologic therapy for cluster headache; AND

  Note: Examples of standard prophylactic pharmacologic therapies for cluster headache include lithium, verapamil, melatonin, frovatriptan, prednisone, suboccipital steroid injection, topiramate, and valproate.
- **13.** Patient has had inadequate efficacy or has experienced adverse event(s) severe enough to warrant discontinuation of the standard prophylactic pharmacologic therapy, according to the prescriber.

12. Migraine Headache Prevention. Approve Emgality for 1 year if the patient meets the following criteria (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has ≥ 4 migraine headache days per month (prior to initiating a migraine-preventative medication); AND
- **C)** Patient has tried at least two standard prophylactic pharmacologic therapies, each from a different pharmacologic class; AND

  Note: Examples of standard prophylactic pharmacologic therapies for migraine include angiotensin receptor blocker, angiotensin converting enzyme inhibitor, anticonvulsant, β-blocker, calcium channel blocker, tricyclic antidepressant, other antidepressant.
- **D)** Patient meets ONE of the following criteria (i, ii, or iii):
  - **i.** The patient has had inadequate efficacy to both of those standard prophylactic pharmacologic therapies, according to the prescriber; OR
  - **ii.** The patient has experienced adverse event(s) severe enough to warrant discontinuation of both of those standard prophylactic pharmacologic therapies, according to the prescriber; OR
  - **iii.** The patient has had inadequate efficacy to one standard prophylactic pharmacologic therapy and has experienced adverse event(s) severe enough to warrant discontinuation to another standard prophylactic pharmacologic therapy, according to the prescriber; AND
- **E)** Patient meets ONE of the following (i or ii):
  - **i.** Patient has tried at least one triptan therapy; OR
  - **ii.** Patient has a contraindication to triptan(s) according to the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Emgality has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-

coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

10. **Acute Treatment of Migraine.** Emgality has not been studied for the acute treatment of migraine.

11. **Combination Therapy with Aimovig® (erenumab-aooe injection for subcutaneous use), with Ajovy® (fremanezumab-vfrm injection for subcutaneous use), or Vyepti™ (eptinezumab-jjmr injection for intravenous use).** Ajovy, Aimovig, Emgality, and Vyepti are calcitonin gene-related peptide (CGRP) antagonists for migraine prevention and have not been studied for use in combination with another agent in the same class.[8-10]

12. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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110. Ajovy® injection for subcutaneous use [prescribing information]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; January 2020.
111. Vyepti™ injection for intravenous use [prescribing information]. Bothell, WA: Lundbeck Seattle BioPharmaceuticals, Inc.; February 2020.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	09/28/2018
Annual revision	No change to criteria.	05/29/2019
Selected revision	Addition of criteria for episodic cluster headache treatment.	07/03/2019
Selected revision	For the FDA-approved indication of Episodic Cluster Headache Treatment, approval criteria was changed from requiring a trial of at least two standard prophylactic pharmacologic therapies to requiring a trial of at least one standard prophylactic pharmacologic therapy. The prescriber still needs to attest to the patient having had inadequate efficacy or having experienced adverse event(s) severe enough to warrant discontinuation of the standard prophylactic pharmacologic therapy.	10/23/2019
Annual revision	For the Condition Not Recommended for Approval of combination therapy, Vyepti was added to the list of injectable calcitonin gene-related peptide inhibitors.	04/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Calcitonin Gene-Related Peptide Inhibitors – Vyepti™ (eptinezumab-jjmr injection for intravenous use – Lundbeck)

DATE REVIEWED: 03/25/2020; selected revision 04/15/2020

OVERVIEW

Vyepti, a calcitonin gene-related peptide (CGRP) inhibitor, is indicated for the preventive treatment of migraine in adults.[1] Vyepti is a humanized monoclonal antibody produced in *Pichia pastoris* yeast cells by recombinant DNA technology. Vyepti binds to the CGRP ligand and blocks its binding to the CGRP receptor. The recommended dosage is 100 mg administered by intravenous (IV) infusion over approximately 30 minutes once every 3 months; however, some patients may benefit from a dosage of 300 mg IV once every 3 months. Vyepti must be administered by a healthcare provider.

Disease Overview

Migraine is a common, chronic condition marked by paroxysmal, unilateral attacks of moderate-to-severe throbbing headache which is aggravated by routine physical activity (e.g., walking or climbing stairs) and associated with nausea, vomiting, and/or photophobia and phonophobia.[2] Migraine headache episodes typically last 4 to 72 hours if untreated. Migraine affects approximately 15% of US adults.[3] Migraines have been defined as chronic or episodic. Chronic migraine is described by the International Headache Society as headache occurring on ≥ 15 days/month for > 3 months and has the features of migraine headache on ≥ 8 days/month.[2] Episodic migraine is characterized by headaches that occur < 15 days/month.[4] Patients with episodic migraine may transform to chronic migraine over time at a rate of about 2.5% of episodic-migraine patients/year. Potential strategies for preventing migraine transformation include preventing and treating headaches, lifestyle modifications, or effective management of comorbidities (e.g., obesity, obstructive sleep apnea, depression, anxiety). Episodic migraine is more common than chronic migraine; however, chronic migraine is associated with a markedly greater personal and societal burden.

Guidelines

An updated assessment of the **preventive and acute treatment of migraine** by the **American Headache Society** (2018) reaffirms previous migraine guidelines.[5] Patients with migraine should be considered for preventive treatment when attacks significantly interfere with patients' daily routines despite acute treatment; frequent attacks (≥ 4 monthly headache days); contraindication to, failure, overuse, or adverse events with acute treatments; or patient preference. Before developing a preventive treatment plan, the appropriate use (e.g., drug type, route and timing of administration, frequency) of acute treatments should be initiated and coupled with education and lifestyle modifications. All patients with migraine should be offered a trial of acute treatment. Based on the level of evidence for efficacy and the American Academy of Neurology (AAN) scheme for classification of evidence, the following oral treatments have established efficacy and should be offered for migraine prevention: antiepileptic drugs (divalproex sodium, valproate sodium, topiramate [not for women of childbearing potential without a reliable method of birth control]); beta-blockers (metoprolol, propranolol, timolol); and frovatriptan (for short-term preventive treatment of menstrual migraine).[6] The following treatments are probably effective and should be considered for migraine prevention: antidepressants (amitriptyline, venlafaxine); beta-blockers (atenolol, nadolol); and angiotensin receptor blockers (candesartan).

Four injectable preventive therapies for migraine are mentioned in the AHS consensus statement: Botox® (onabotulinumtoxinA injection) and three monoclonal antibodies targeting CGRP (Aimovig, Ajovy® [fremanezumab-vfrm injection], and Emgality® [galcanezumab-gnlm injection]).[5] The update notes that a CGRP inhibitor should only be initiated in patients who are diagnosed with migraine, have ≥ 4 migraine headache days per month, and have intolerance or inadequate response to 6-week trials of at least two traditional oral migraine preventive medications. Additional criteria apply depending on the number and severity of monthly headache days. Clinical judgment may result in an emerging treatment being added to one or more established treatments. If initiating treatment with a CGRP inhibitor in a patient already on a preventive treatment, it is appropriate to add the CGRP inhibitor to the existing regimen and make no other changes until the effectiveness of the CGRP inhibitor is determined since the risk of interactions between traditional oral migraine preventive medications and the CGRP inhibitors is minimal or nonexistent. Making a decision regarding continuation of therapy for a CGRP inhibitor requires a trial of the medication for at least 3 months, and treatment should be continued only if benefits can be documented during that time (e.g., reduction in mean monthly headache days of ≥ 50% relative to the pretreatment baseline). Since migraine may improve or remit over time, it is important to reevaluate therapeutic response and, if possible, taper or discontinue

treatment if patients no longer meet the criteria for offering preventive treatment. However, once control is established, the decision to discontinue or taper treatment should be a shared decision between patient and clinician.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Vyepti. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vyepti is recommended in those who meet the following criteria:

FDA-Approved Indications

13. Migraine Headache Prevention. Approve Vyepti for 1 year if the patient meets the following criteria (A, B, C, and D):

14. Patient is ≥ 18 years of age; AND

15. Patient has ≥ 4 migraine headache days per month (prior to initiating a migraine-preventative medication); AND

16. Patient has tried at least two standard prophylactic pharmacologic therapies, each from a different pharmacologic class (e.g., angiotensin receptor blocker, angiotensin converting enzyme inhibitor, anticonvulsant, β-blocker, calcium channel blocker, tricyclic antidepressant, other antidepressant), and meets ONE of the following criteria (i, ii, or iii):

- **i.** The patient has had inadequate efficacy to both of those standard prophylactic pharmacologic therapies, according to the prescriber; OR
- **ii.** The patient has experienced adverse event(s) severe enough to warrant discontinuation of both of those standard prophylactic pharmacologic therapies, according to the prescriber; OR
- **iii.** The patient has had inadequate efficacy to one standard prophylactic pharmacologic therapy and has experienced adverse event(s) severe enough to warrant discontinuation to another standard prophylactic pharmacologic therapy, according to the prescriber; AND

17. Patient meets ONE of the following (i or ii):

- **i.** Patient has tried at least one triptan therapy; OR
- **ii.** Patient has a contraindication to triptan(s) according to the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Vyepti has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

2. Acute Treatment of Migraine. Clinical data is currently lacking for the use of Vyepti in the acute treatment of migraine.

3. Cluster Headache, Treatment or Prevention. Vyepti has not been studied in patients with cluster headache. The pivotal trials of Vyepti excluded patients with this condition.[7,8]

4. Combination Therapy with Aimovig® (erenumab-aooe injection for subcutaneous use), Ajovy® (fremanezumab-vfrm injection for subcutaneous use) or Emgality® (galcanezumab-gnlm injection for subcutaneous use). Aimovig, Ajovy, Emgality, and Vyepti are calcitonin gene-related peptide (CGRP) inhibitors for migraine prevention and have not been studied for use in combination with another agent in the same class.[9-11]

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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22. Emgality® injection for subcutaneous use [prescribing information]. Indianapolis, IN: Eli Lilly and Company; December 2019.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	03/25/2020
Selected revision	Throughout the criteria, "prescribing physician" was changed to "prescriber". For the Condition Not Recommended for Approval of cluster headache, "treatment or prevention" was added to clarify the intent.	04/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Cardiology – Corlanor Prior Authorization Policy

- Corlanor® (ivabradine tablets and oral solution – Amgen)

REVIEW DATE: 05/20/2020

OVERVIEW

Corlanor, a hyperpolarization-activated cyclic nucleotide-gated channel blocker, is indicated to reduce the risk of hospitalization for worsening heart failure (HF) in adults with stable, symptomatic chronic HF with left ventricular ejection fraction (LVEF) ≤ 35%, who are in sinus rhythm with a resting heart rate ≥ 70 beats per minute (bpm) and either are receiving maximally tolerated doses of beta blockers or have a contraindication to beta blocker use.[1] Corlanor is also indicated for the treatment of stable symptomatic HF due to dilated cardiomyopathy in pediatric patients ≥ 6 months and older, who are in sinus rhythm with an elevated heart rate.

Clinical Efficacy

The efficacy of Corlanor was established in a randomized, event-driven, multinational, double-blind, parallel-group pivotal trial called SHIFT (Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial) that compared Corlanor with placebo, in addition to standard HF therapies, in adults with stable New York Heart Association (NYHA) class II to IV HF, a reduced LVEF, and a resting heart rate of rate 70 bpm (n = 6,558).[1,2] The occurrence of the primary endpoint (a composite of the first occurrence of either hospitalization for HF or worsening HF or cardiovascular [CV] death) was reduced with Corlanor compared with placebo[1,2]

A randomized, multicenter, double-blind, placebo-controlled, Phase II/III, 12-month trial evaluated the effects of Corlanor on heart rate in children who were ≥ 6 months to < 18 years of age, with symptomatic dilated cardiomyopathy (n = 116).[1,17] Patients had a history of class II or IV symptomatic HF (NYHA functional class or Ross classification) and a LVEF ≤ 45% who were receiving stable treatment for chronic HF. Also, patients had to be clinically stable for ≥ 4 weeks and be optimized on medical therapy and have a resting heart rate in the normal range for age. The mean patient age was 5.8 ± 4.9 years.[17] The target heart rate reduction was achieved at the end of the titration period in a higher number of patients who received Corlanor compared with placebo (72% vs. 16%).[1] Of note, dilated cardiomyopathy comprises approximately one-half of all cardiomyopathies in children.[17] The overall incidence of pediatric dilated cardiomyopathy is low; however, it is more common in children < 1 year of age (44 cases per million/year) compared with children ≥ 3 years of age (3.4 cases per million/year).

Guidelines

In 2017 the American College of Cardiology (ACC), American Heart Association (AHA), and the Heart Failure Society of America published a focused update for the management of heart failure.[14] Regarding Corlanor it is stated that the agent can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA Class II to III) stable chronic HF with reduced ejection fraction (LVEF ≤ 35%) who are receiving guideline-directed evaluation and management, including a beta-blocker at the maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 beats per minute or greater at rest. Due to the well-proven mortality benefits of beta blocker therapy, it is important to initiate and up-titrate these agents to target doses, as tolerated, prior to evaluating resting heart rate for consideration of Corlanor.

Other Uses with Supportive Evidence

Inappropriate sinus tachycardia is defined as a sinus heart rate > 100 bpm at rest (with a mean 24-hour heart rate > 90 bpm not due to primary causes) and is associated with distressing symptoms such as palpitations, weakness, dizziness and syncope.[11] The condition is believed to be chronic in many cases. The mechanisms causing inappropriate sinus tachycardia are not distinctly known but underlying diseases that can result in this syndrome include increased sinus node automaticity, beta-adrenergic hypersensitivity, and decreased parasympathetic activity. There is a paucity of long-term, prospective, placebo-controlled trials of any agents that show substantial improvement in outcomes, and syndromes may persist despite heart rate control. Very few medications have solid evidence supporting benefits for this condition. Beta-blockers are not usually effective. Other treatments have been suggested (e.g., fludrocortisone, volume expansion, clonidine, and erythropoietin). Some data with Corlanor note improvement in symptoms and increased exercise performance.[11-13,15,19-21] The 2015 Heart Rhythm Society Expert Consensus Statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope state that Corlanor can be useful for treating patients with inappropriate sinus tachycardia.[11] Additionally, the 2015 American College of Cardiology, American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Rhythm Society also state that Corlanor is reasonable for ongoing management in patients with symptomatic inappropriate sinus tachycardia (class IIa recommendation).[12] Also, the guidelines state that the combination of beta blockers and Corlanor may be considered for the ongoing management of patients with inappropriate sinus tachycardia (class IIb recommendation).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Corlanor. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Corlanor is recommended in those who meet the following criteria:

FDA-Approved Indications

14. Heart Failure (HF). Approve for 1 year if the patient meets the following criteria (A, B and C):

- **A)** Patient is ≥ 18 years of age; AND
- **B)** The patient has a left ventricular ejection fraction (LVEF) ≤ 35% currently or prior to initiation of Corlanor therapy; AND
- **C)** The patient meets one of the following (i or ii):
  - **iii.** The patient has tried or is currently receiving one beta blocker for heart failure treatment. Note: Examples of beta blockers are metoprolol succinate sustained-release, carvedilol, bisoprolol, and Coreg CR® (carvedilol extended-release capsules); OR
  - **iv.** The patient has a contraindication to use of beta blocker therapy. Note: Examples that are contraindications to use of beta blockers are bronchospastic disease such as chronic obstructive pulmonary disease (COPD) and asthma, severe hypotension or bradycardia.

2. Heart Failure due to Dilated Cardiomyopathy. Approve for 1 year if the patient is < 18 years of age.

Other Uses with Supportive Evidence

3. Inappropriate Sinus Tachycardia. Approve for 1 year.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Corlanor is recommended in those who meet the following criteria:

64. Stable Angina Pectoris, in Patients Without Chronic Heart Failure. Corlanor has been studied as a treatment for stable angina pectoris but further data are needed.[4-8,18] US guidelines addressing stable angina do not include Corlanor.[9-10,15-16]

65. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	05/23/2018
Annual Revision	The oral solution was added to with the same approval criteria as those applied to Corlanor tablets. The heading "Cardiology" was put in the name of this policy. **Chronic Heart Failure:** This criteria set was revised to remove the distinctions that differed in criteria for patients who are not receiving Corlanor (initial therapy) and among those who are currently receiving Corlanor. Criteria were revised so that these two clinical scenarios are addressed in one criteria set. The criterion that the patient is in sinus rhythm with a resting heart rate of ≥ 70 beats per minute was removed, which only impacted patients who were to receive therapy initially. To address both clinical	05/08/2019

	scenarios, the phrase "currently or prior to initiation of Corlanor therapy" was added to the criterion that requires patients to have a left ventricular ejection fraction ≤ 35%. Also, due to the new indication in children (addressed below), the descriptor of "adults" was added to the chronic heart failure diagnosis. **Heart failure due to Dilated Cardiomyopathy, Children.** This diagnosis was added to approve for 1 year based on its new FDA-approved indication for use.	
Annual Revision	The following changes were made: **a. Heart Failure (Adults):** The terms of "Chronic" and "Adults" were removed from the listing of the indication. A criterion was added that the patient is ≥ 18 years of age. For the criteria that requires that the patient has tried or is currently receiving one beta blocker for heart failure treatment, the examples of beta blockers removed from the criteria and put in a note. Also, the reasons provided on why use of beta blocker therapy is contraindicated was moved from the criteria to a note. **b. Heart Failure (Children).** The term "Children" was removed from the wording of the indication "Heart Failure due to Dilated Cardiomyopathy, Children." A criterion was added that the patient is < 18 years of age.	05/20/2020

PRIOR AUTHORIZATION POLICY

POLICY: Cardiology – Zontivity Prior Authorization Policy
- Zontivity® (vorapaxar tablets – Aralez Pharmaceuticals)

REVIEW DATE: 10/14/2020

OVERVIEW

Zontivity, a protease-activated receptor-1 antagonist, is indicated for the reduction of thrombotic cardiovascular (CV) events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD).[1] Zontivity has been shown to reduce the rate of a combined endpoint of CV death, MI, stroke, and urgent coronary revascularization. There is no experience with the use of Zontivity alone as the only administered antiplatelet agent. Studies involving Zontivity involved adding the agent to aspirin and/or clopidogrel. Use Zontivity with aspirin and/or clopidogrel according to indicated uses or the standard of care. The clinical use of Zontivity with other antiplatelet medications is limited. In a subgroup analyses of the pivotal data, patients weighing < 60 kg who received Zontivity did not have a favorable outcome regarding the primary composite endpoint of CV death, MI, stroke, or urgent coronary revascularization.[1,2]

Guidelines

In 2016 and American Heart Association and the American College of Cardiology published a guidelines on the management of patients with lower extremity peripheral artery disease (PAD).[3] The guidelines state that the overall clinical benefit of Zontivity added to existing antiplatelet therapy in patients with symptomatic PAD is uncertain.

Safety

Zontivity has a Boxed Warning regarding the risk of bleeding. Zontivity is contraindicated in patients with a history of stroke, transient ischemic attack (TIA), or intracranial hemorrhage (ICH). Antiplatelet medications, including Zontivity, increased the risk of bleeding, including ICH and fatal bleeding.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zontivity. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zontivity is recommended in patients who meet the following criteria:

FDA-Approved Indication

15. Patient with a Previous Myocardial Infarction (MI) or Peripheral Arterial Disease (PAD). Approve for 3 years if the patient meets the following criteria (A, B and C):

O) Patient is receiving Zontivity in combination with aspirin and/or clopidogrel; AND

P) Patient has been determined to be at high risk for future thrombotic events as determined by the prescriber; AND

Note: Examples of high risk include that the patient has experienced multiple myocardial infarctions, has undergone many urgent coronary revascularization procedures, has had placement of coronary artery stents, or the patient has other concomitant diseases that increase cardiovascular risk such as diabetes.

Q) The patient weighs ≥ 60 kg.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zontivity is not recommended in the following situations:

66. Acute Coronary Syndrome (ACS) that Occurred Recently (within < 14 days). In the TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in acute coronary syndrome) study, adding Zontivity to standard therapy in those who experienced an ACS increased the risk of major bleeding and did not result in clinical benefits.

67. Patient with a Prior History of Stroke, Transient Ischemic Attack (TIA), or Intracranial Hemorrhage (ICH). Zontivity is contraindicated for use in patients with a history of stroke, TIA or ICH due to an increased risk of ICH in this population.

68. Concurrent Use of Effient® (prasugrel tablets) or Brilinta® (ticagrelor tablets). There is limited clinical experience involving use of Zontivity with antiplatelet agents (e.g., Effient, Brilinta) other than aspirin and/or clopidogrel.

69. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	ReviewDate
Annual Revision	No criteria changes.	10/10/2018
Annual Revision	No criteria changes.	10/09/2019
Annual Revision.	Added the header "Cardiology" to the *Zontivity Prior Authorization Policy*. In the criteria, the phrase "prescribing physician" was changed to "prescriber". Also, examples of clinical scenarios associated with a high risk of thrombotic events was moved from the criteria to a Note.	10/14/2020

PRIOR AUTHORIZATION POLICY

POLICY: Chelating Agents – Chemet® (succimer capsules – Lannett Company, Inc., for Recordati Rare Diseases, Inc.)

DATE REVIEWED: 04/22/2020

OVERVIEW

Chemet, a heavy metal chelator, is indicated for the treatment of lead poisoning in pediatric patients with blood lead levels > 45 mcg/dL.[1] Chemet is not indicated for prophylaxis of lead poisoning in a lead-containing environment; the use of Chemet should be accompanied by identification and removal of the source of the lead exposure. Safety and efficacy of Chemet in children < 12 months of age have not been established. The course of therapy is 19 days; if indicated, a repeat course may be given with a minimum of 2 weeks between courses, unless blood lead levels indicate the need for more prompt treatment. The chemical name for Chemet is *meso* 2,3-dimercaptosucininc acid (DMSA).

Lead, mercury, arsenic, and iron account for most cases of diagnosed heavy metal poisoning in the US.[2] Most cases of lead poisoning are in children who swallow lead-based paint in homes or toys; other causes include water carried through pipes made of lead or containing lead solder. Children are especially susceptible to the toxic effects of lead, which may affect the developing brain and nervous system, potentially causing lower IQs, learning difficulties, hearing loss, and behavior difficulties. In adults, lead poisoning can cause high blood pressure and kidney damage.

Arsenic is a naturally-occurring substance; in some areas of the world, low-level arsenic exposure occurs because of the presence of arsenic in ground water.[2] Accidental poisoning accounts for the majority of acute arsenic toxicity.[3] Patients may develop muscle weakness, numbness and tingling in their arms and legs, skin changes (darkening or discoloration, redness, swelling, and hyperkeratosis), sensory and motor nerve damage, and cancer if they are exposed to lower levels of arsenic over a long period of time.[2,4] Symptoms of acute poisoning include gastrointestinal (GI) symptoms, such as profuse vomiting and diarrhea; shock and coma can follow.[2] The Agency for Toxic Substances and Disease Registry (ATSDR) states that patients with severe arsenic poisoning must be hospitalized.[7] Chelation therapy can curtail the distribution of arsenic in the body and reduce the body burden. Oral chelators, such as Chemet, have been used with success. There are case reports to support the use of DMSA in acute arsenic poisoning.[3,8] The patients' clinical status improved with DMSA therapy and urine arsenic levels decreased with therapy.

Mercury poisoning can result from vapor inhalation, mercury ingestion, mercury injection, and absorption of mercury through the skin.[5] Symptoms of mercury poisoning depends on the type of mercury exposure and severity of exposure: organic mercury (antiseptics, bactericidals, fungicides, insecticides), inorganic mercury (chemical laboratory work, disinfectants, explosives, fur hat processing), and elemental mercury (thermometers, batteries, dental amalgams, fluorescent lamps). The primary sources of inorganic mercury exposure in humans are from contaminated fish and industrial chemicals.[2,5] Chronic and intense acute mercury exposure cause cutaneous (e.g., erythema of the palms and soles, desquamating rash) and

neurologic symptoms (e.g., visual loss, extremity numbness, hearing loss, and ataxia). Other effects of mercury exposure include GI effects, weight loss, fatigue, lung injury, and kidney damage.[2] The ATSDR notes that patients with serious mercury exposure must be hospitalized.[9] Chelation should be considered for any symptomatic patient with a clear history of acute elemental mercury exposure. The decision to chelate is less clear in asymptomatic patients with elevated urine mercury levels.[10] Oral chelators, such as Chemet, have been used successfully for the treatment of acute mercury intoxication/poisoning.[9] The World Health Organization (WHO) recommends that urine mercury concentration should not exceed 50 mcg/g creatinine.[11]

Several case reports have demonstrated the effectiveness of DMSA therapy for treatment of acute mercury poisoning.[12-15] All of the patients exhibited symptoms consistent with mercury poisoning and were treated in a hospital setting. DMSA therapy resulted in reduction of mercury levels and improved symptomatology.

Treatment Recommendations
Treatment of heavy metal poisoning includes removing the patient from the source of the metal and treating the patient's symptoms.[2] Diagnosis includes the patient's history, symptoms, and blood or urine tests.[2,4,5] Treatment of acute metal poisoning involves emergency care and generally requires the use of chelating agents, such as DMSA.[6] The chemical name for Chemet is DMSA. (Note: the chemical name, DMSA, will be used to describe the case reports in this document because it is unclear if the FDA-approved Chemet product was used).

POLICY STATEMENT
Prior authorization is recommended for prescription benefit coverage of Chemet. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Chemet as well as the monitoring required for adverse events, approval requires Chemet to be prescribed by, or in consultation with, a physician who specializes in the condition being treated..

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts and/or laboratory data.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Chemet is recommended in those who meet the following criteria:

FDA-Approved Indications

16. **Acute Lead Poisoning.** Approve for 2 months if the patient meets the following criteria (A, B, C, and D):
    - **A)** The patient is between the age of 12 months and 18 years; AND
    - **B)** Prior to starting Chemet therapy, the patient's blood lead level was > 45 micrograms/deciliter (mcg/dL) **[documentation required]**; AND
    - **C)** Chemet is being used for treatment of acute lead poisoning and not as prophylaxis against lead poisoning in a lead-containing environment; AND
    - **D)** Chemet is prescribed by, or in consultation with, a professional experienced in the use of chelation therapy (e.g., a medical toxicologist or a poison control center specialist).

Other Uses with Supportive Evidence

17. **Acute Arsenic Intoxication/Poisoning.** Approve for 1 month if the patient meets the following criteria (A and B):
    - **A)** The patient was recently initiated on Chemet therapy in the hospital and further treatment is needed to finish the course of therapy; AND
    - **B)** Chemet is prescribed by, or in consultation with, a professional experienced in the use of chelation therapy (e.g., a medical toxicologist or a poison control center specialist).

18. **Acute Mercury Intoxication/Poisoning.** Approve for 1 month if the patient meets the following criteria (A and B):
    - **A)** The patient was recently initiated on Chemet therapy in the hospital and further treatment is needed to finish the course of therapy; AND
    - **B)** Chemet is prescribed by, or in consultation with, a professional experienced in the use of chelation therapy (e.g., a medical toxicologist or a poison control center specialist).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Chemet has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below.

70. **Use of Chemet in Conjunction with other Chelators (e.g., calcium disodium versenate injection [$CaNa_2EDTA$], dimercaprol injection [British anti-Lewisite {BAL}]).**
    In patients with acute lead poisoning, data on the concomitant use of Chemet with $CaNa_2EDTA$ with or without BAL are not available and such use is not recommended.[1]

71. **Chelation of Heavy Metals to Treat Chronic Medical and/or Psychiatric Conditions.**
    Chelation of heavy metals has been advertised as a viable treatment for numerous conditions: treatment of intermittent claudication; treatment or management of symptoms of autism; prevention or cure of neurodegenerative conditions such as Alzheimer's disease; use in Parkinson's disease; treatment of macular degeneration.[2] There is no evidence to show that chelators work in these conditions. Furthermore, unapproved uses of chelation therapy have resulted in harm and even death.

    Chelation of heavy metals is also one of several popular interventions in children with autism spectrum disorders.[2] The FDA notes chelation therapies for the treatment of autism to be associated with significant health risks and does not approve such use.[16]

72. **Chronic Arsenic Exposure.**
    Use of chelation therapy following chronic exposure to inorganic arsenic may accelerate metal excretion, but potential therapeutic efficacy in terms of decreased morbidity and mortality is largely unestablished.[17]

    In a prospective, randomized-controlled trial, 21 patients with chronic arsenicosis due to drinking arsenic-contaminated subsoil water were randomized to receive DMSA (1,400 mg/day or 100 mg/m^2 in four divided doses for 1 week and then 1,050 mg/day or 750 mg/m^2 in three divided doses for 2 weeks; repeat the regimen after 3 weeks) or placebo.[18] The patients had history of drinking arsenic-contaminated water (50 mcg/L or $\geq$ 0.05 mg/L) for at least 2 years and clinical signs/symptoms of chronic arsenicosis. Similar improvement in the clinical score was observed in the DMSA and placebo groups. Furthermore, urinary arsenic excretion before treatment and at 48 hours and 72 hours post-

treatment were similar between the two groups. The investigators concluded that DMSA did not result in clinical or biochemical benefit in patients with chronic arsenicosis.

In another case report involving a 39 year old woman with arsenic poisoning (urine arsenic level was 2,000 mcg/L; normal level is < 10 mcg/L), DMSA 600 mg three times a day (TID) for 45 days did not significantly affect the clearance of arsenic or clinical outcome.[19] During the 45-day course, the patient stopped therapy for a total of 13 days (unknown reason).

73. Chronic Mercury Exposure.

The American Academy of Pediatrics notes there is no scientific evidence behind the use of chelation therapy to improve nervous system symptoms of chronic mercury toxicity.[16] Use of chelation therapy following chronic exposure to inorganic mercury may accelerate metal excretion, but potential therapeutic efficacy in terms of decreased morbidity and mortality is largely unestablished.[17]

In a randomized, double-blind, parallel-group, placebo-controlled study in Sweden, 20 patients were randomized to receive DMSA 20 mg/kg/day in three divided doses or placebo for 14 days.[20] These patients experienced symptoms that were allegedly associated with amalgam fillings for at least 6 months. DMSA therapy resulted in increased urinary excretion of mercury and blood mercury levels were decreased. However, there were no statistically significant changes in any of the symptoms. The investigators concluded that although urinary excretion of mercury was increased during DMSA treatment, chelating therapy did not alleviate symptoms allegedly attributable to mercury from amalgam fillings.

Cao and colleagues reported the effects of Chemet in reducing blood mercury levels in children 12 to 33 months of age.[21] The original study was to evaluate the use of Chemet for lead poisoning; the investigators used the blood samples for the lead study and measured the mercury levels. Blood mercury concentrations were measured one week before randomization and treatment, at one week after treatment initiation, and after three courses of treatment. Mercury was not detected/quantified in any of the blood samples. At one week of treatment, organic mercury concentration decreased 8% in the Chemet group, but remained the same in the placebo group (P = 0.04). However, the investigators suggested that the difference was not due to a reduction in the Chemet group but rather, Chemet therapy prevented a rise in the blood mercury concentration as seen in the placebo group. Chemet therapy did not reverse the accumulation of organic mercury over multiple courses over 5 months.

74. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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History

Type of Revision	Summary of Changes	Date Reviewed
Annual revision	No criteria changes.	04/25/2018
Annual revision	No criteria changes.	04/19/2019
Annual revision	No criteria changes.	04/22/2020

PRIOR AUTHORIZATION POLICY

POLICY: Chelating Agents – Iron Chelators (Oral) Prior Authorization Policy

- Exjade® (deferasirox tablets for suspension – Novartis; generics)
- Jadenu® (deferasirox tablets – Novartis; generics)
- Jadenu® Sprinkle (deferasirox granules for oral use – Novartis)
- Ferriprox® (deferiprone tablets and oral solution – ApoPharma USA)

REVIEW DATE: 06/17/2020

OVERVIEW

Iron chelating therapy should be considered in all patients who require long-term blood transfusions.[5] Patients with sickle cell disease, myelodysplastic syndromes (MDS), thalassemia major, Diamond-Blackfan anemia, aplastic anemia, and other congenital and acquired forms of refractory anemia (e.g., hereditary hemochromatosis) may require regular blood transfusions and as a result may require iron chelation therapy. This is because the body does not have an efficient mechanism to excrete iron.[4] In patients requiring multiple blood transfusions, iron accumulates and is deposited into multiple organ systems. The long term consequences of chronic iron overload include multiple organ dysfunction (e.g., heart, liver) and/or organ failure. Iron chelation therapy is necessary to prevent organ failure and decrease mortality. In the US, it is estimated that approximately 25,000 patients are transfusion dependent due to various causes such as sickle cell disease and refractory anemias.[7]

Serum ferritin level measurements are the laboratory parameter most often used to assess the iron burden and response to chelation therapy.[4] Sustained serum ferritin levels > 2,500 mcg/L are associated with organ toxicity and death. Most chelation regimens strive to achieve the goal of ferritin levels < 2,500 mcg/L. Trends in ferritin level are useful in monitoring the direction of body iron loading, but it may not predict cardiac iron loading.[6] Long-term elevations in ferritin levels predict cardiac mortality, with ferritin levels > 2,500 mcg/L indicating a higher cardiac risk; however, there is no threshold effect, so a ferritin level of 1,000 mcg/L could indicate a risk. Cardiac iron levels have a better predictive value of heart failure.

Exjade, Jadenu (granules and tablets), and Ferriprox are orally administered iron chelators used for the treatment of iron overload.[1-3] Exjade and Jadenu have the same chemical entity (deferasirox) in different formulations.[1-2] Deferoxamine is an intravenously (IV) administered iron chelator that is not covered under this prior authorization policy. Both Exjade and Jadenu products have Limitations of Use that safety and efficacy has not been established when each of these agents are used in combination with other iron chelation therapy.

Ferriprox is indicated for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate.[3] Ferriprox approval was based on a reduction in serum ferritin levels. There are no controlled trials demonstrating a direct treatment benefit, such as an improvement in disease-related symptoms, functioning, or increased survival. Safety and effectiveness of Ferriprox for the treatment of transfusional iron overload in patients with other chronic anemias have not been established.

Exjade and Jadenu (granules and tablets) have the following FDA-approved indications[1-2]:

- Treatment of chronic iron overload due to blood transfusions (transfusion iron overload) in patients ≥ 2 years of age. Exjade/Jadenu therapy should be considered when a patient has evidence of chronic transfusional iron overload (e.g., at least 20 units of packed red blood cells for a 40 kg person or more) and a serum ferritin consistently > 1,000 mcg/L.
- Exjade and Jadenu are also indicated for the treatment of chronic iron overload in patients ≥ 10 years of age with non-transfusion-dependent thalassemia (NTDT) syndromes and with a liver iron concentration (LIC) of at least 5 milligrams of iron per gram of liver dry weight (mg Fe/g dw) and a serum ferritin > 300 mcg/L. This indication is based on achievement of an LIC < 5 mg Fe/g dw. An improvement in survival or disease-related symptoms has not been established.
- Limitations of Use: Controlled trials of Exjade and Jadenu with myelodysplastic syndrome (MDS) and chronic iron overload due to blood transfusions have not been performed. The safety and efficacy of Exjade and Jadenu when administered with other iron chelation therapy have not been established.

EFFICACY

A 5-year multicenter, randomized, open-label trial assessed the efficacy of Ferriprox compared with deferoxamine intravenous (IV) treatment in patients with sickle cell disease.[11] Patients (n = 60) were > 13 years of age and had serum ferritin concentration between 800 to 3,000 mcg/L. By Year 5, 36.6% of patients treated with Ferriprox achieved serum ferritin levels < 400 mcg/L compared with 3.3% of patients treated with deferoxamine. Overall survival did not differ significantly between the two groups after 5 years or 10 years. A Phase III study is underway comparing the efficacy of Ferriprox vs. Exjade/Jadenu in pediatric patients with transfusion-related iron overload due to thalassemia, sickle cell disease, and other conditions.[12] Studies with Ferriprox use in pediatric patients for various iron overload conditions have been conducted in other countries.[13]

Iron overload in thalassemia intermedia is mainly due to increased intestinal absorption of iron due to chronic anemia.[9] Transfusions play a minor role in iron overloading in these patients, but iron chelation therapy is indicated for thalassemia intermedia. A 5-year randomized, open-label, long-term trial was

conducted in patients (n = 88) with thalassemia intermedia comparing Ferriprox with deferoxamine IV treatment. After 5 years there were no statistically significant differences between Ferriprox and deferoxamine in the decrease in mean serum ferritin levels and overall survival. There are data available from other studies as well with Ferriprox use in iron-loaded non-transfusion dependent thalassemias.[10]

The three pivotal studies for Exjade/Jadenu included patients with β-thalassemia, chronic anemias, myelodysplastic syndromes, sickle cell disease, Diamond-Blackfan syndrome and other congenital or acquired anemias.[1,2] The prospective EPIC study (Evaluation of Patients' Iron Chelation with Exjade) included patients with thalassemia (~70%), myelodysplastic syndrome (20%), aplastic anemia (7%), sickle cell disease (5%) and other rare anemias such as red cell aplasia and hemolytic anemias (~2.5%).[14] Baseline median serum ferritin levels in all subgroups were > 2,500 mcg/L. Overall there was a significant reduction in serum ferritin level from baseline (-264 ng/mL) in all subgroups, except sickle cell disease (likely due to low number of patients). The NCCN myelodysplastic syndromes guidelines notes that monitoring serum ferritin levels and aiming to decrease ferritin levels to < 1,000 mcg/L may be useful.[8]

GUIDELINES

The American Heart Association published a consensus statement on cardiovascular function and treatment in β-thalassemia major.[6] Exjade/Jadenu, Ferriprox, and deferoxamine intravenous (IV) iron chelator all remove cardiac iron if given in adequate doses and if patient compliance is good. Optimal therapy must be tailored to each patient. In patients with detectable, asymptomatic cardiac iron overload, the following are noted: retrospective studies suggest that Ferriprox monotherapy may offer superior cardiac protection and improve survival compared with deferoxamine IV chelator. The AHA recommends the use of Ferriprox monotherapy in patients with cardiac siderosis and it is also suitable for patients with reduced left ventricular ejection fraction (LVEF) or asymptomatic left ventricular (LV) dysfunction. Exjade/Jadenu monotherapy can be used successfully in patients with detectable cardiac iron and normal cardiac function; however, no change in LVEF was observed in trails. The AHA recommends Exjade/Jadenu for cardiac siderosis, but it is not recommended as first-choice treatment for cardiac iron (T2*) < 6 ms or in patients with reduced LVEF because of the limited data on efficacy. Caution is recommended in the use of Exjade/Jadenu monotherapy to treat cardiac siderosis in patients with high liver iron loading, especially if higher doses are required (> 40 mg/kg/day), as cardiac efficacy may be delayed. The use of combination Ferriprox and deferoxamine therapy is noted as widespread, and this combination is used especially in patients with moderate to severe cardiac iron overload or when LVEF is impaired. Exjade/Jadenu has also been used in combination with deferoxamine. There are limited data available for the combination use of daily Ferriprox with daily Exjade/Jadenu.

The National Comprehensive Cancer Network (NCCN) guidelines for myelodysplastic syndromes (version 2.2020 – February 28, 2020) has the following recommendations under supportive care, for the management of iron overload.[8] For patients with chronic transfusion need, serum ferritin levels and associated organ function should be monitored. It is useful to decrease serum ferritin levels to < 1,000 mcg/L. The NCCN Panel recommends consideration of once-daily deferoxamine subcutaneously or Exjade/Jadenu orally to decrease iron overload (aiming for target ferritin level < 1,000 ng/mL) in lower risk patients with MDS or who are potential transplant candidates and are anticipated to receive > 20 to 30 blood transfusions; and patients with serum ferritin levels > 2,500 ng/mL the aim is to get the levels to < 1,000 ng/mL. The NCCN recommendations notes that a third oral chelating agent, Ferriprox, is available and it was approved based on retrospective analysis of pooled efficacy and safety studies in patients with transfusion-related iron overload refractory to existing chelation therapy. NCCN notes that controversy remains regarding the use of this agent for MDS due to the boxed warning for agranulocytosis.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Exjade, Jadenu (granules and tablets), and Ferriprox. Because of the specialized skills required for evaluation and diagnosis of patients treated with these agents as well as the monitoring required for adverse events and long-term efficacy, approval requires Exjade, Jadenu (granules and tablets), and Ferriprox to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration listed below.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or laboratory data.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of **Ferriprox** is recommended in those who meet the following criteria:

FDA-Approved Indications

19. Iron Overload, Chronic – Transfusion-Related Due to Thalassemia Syndromes. Approve Ferriprox for 1 year if the patient meets the following criteria (A or B):

18. Initial Therapy. Approve Ferriprox if the patient meets all of the following criteria (i and ii):

i. Prior to starting Ferriprox therapy, the serum ferritin level was > 2,500 micrograms/liter [mcg/L]) **[documentation required]**; AND

ii. Ferriprox is prescribed by or in consultation with a hematologist.

19. Patients Currently Receiving Ferriprox. Approve for 1 year if the patient is benefiting from Ferriprox therapy (e.g., reduction in the serum ferritin levels by at least 20% from baseline, stable disease, reduced cardiac iron load), as confirmed by the prescriber.

Other Uses with Supportive Evidence

2. Iron Overload, Chronic – Transfusion – Related Due to Sickle Cell Disease. Approve Ferriprox for 1 year if the patient meets the following criteria (A or B).

A) Initial Therapy. Approve Ferriprox if the patient meets all the following criteria (i and ii):

i. Prior to starting Ferriprox therapy, the patient's serum ferritin level was > 1,000 micrograms/liter (mcg/L) **[documentation required]**; AND

ii. Ferriprox is prescribed by or in consultation with a hematologist.

B) Patients Currently Receiving Ferriprox. Approve for 1 year if the patient is benefiting from Ferriprox therapy for sickle cell disease (e.g., reduction in the serum ferritin levels to < 1,000 mcg/L, stable disease, reduced cardiac iron load), as confirmed by the prescriber.

3. Iron Overload, Chronic – Non-Transfusion-Dependent Thalassemia Syndromes. Approve Ferriprox for 1 year if the patient meets the following criteria (A or B).

A) Initial Therapy. Approve Ferriprox if the patient meets all the following criteria (i, ii, and iii):

i. Prior to starting Ferriprox therapy, the patient's serum ferritin level was > 300 micrograms/liter (mcg/L) **[documentation required]**; AND

ii. Ferriprox is prescribed by or in consultation with a hematologist.

B) Patients Currently Receiving Ferriprox. Approve for 1 year if the patient is benefiting from Ferriprox therapy (e.g., reduction in the serum ferritin levels, stable disease, reduced cardiac iron load), as confirmed by the prescriber.

II. Coverage of **Exjade or Jadenu (granules or tablets)** is recommended in those who meet the following criteria:

FDA-Approved Indications

1. Iron Overload, Chronic – Transfusion-Related. Approve Exjade or Jadenu (granules or tablets) for 1 year if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve Exjade or Jadenu (granules or tablets) if the patient meets all the following criteria (i, ii, and iii):

i. Patient is receiving blood transfusions at regular intervals for various conditions (e.g., thalassemia syndromes, myelodysplastic syndrome, chronic anemia, sickle cell disease); AND

ii. Prior to starting Exjade or Jadenu (granules or tablets) therapy, the patient's serum ferritin level was > 1,000 micrograms/liter (mcg/L) **[documentation required]**; AND

iii. Exjade or Jadenu (granules or tablets) is prescribed by or in consultation with a hematologist.

B) Patients Currently Receiving Exjade or Jadenu (granules or tablets). Approve for 1 year if the patient is benefiting from Exjade or Jadenu (granules or tablets) therapy (e.g., reduction in the serum ferritin levels to < 1,000 mcg/L, stable disease, reduced cardiac iron load), as confirmed by the prescriber.

20. Iron Overload, Chronic – Non-Transfusion-Dependent Thalassemia Syndromes. Approve Exjade or Jadenu (granules or tablets) for 1 year if the patient meets the following criteria (A or B).

A) Initial Therapy. Approve Exjade or Jadenu (granules or tablets) if the patient meets all the following criteria (i and ii):

i. Prior to starting Exjade or Jadenu (granules or tablets) therapy, the patient's serum ferritin level was > 300 micrograms/liter (mcg/L) **[documentation required]**; AND

ii. Exjade or Jadenu (granules or tablets) is prescribed by or in consultation with a hematologist.

B) Patients Currently Receiving Exjade or Jadenu (granules or tablets). Approve for 1 year if the patient is benefiting from Exjade or Jadenu (granules or tablets) therapy (e.g., reduction in the serum ferritin levels, stable disease, reduced iron load), as confirmed by the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Exjade, Jadenu (granules or tablets), and Ferriprox have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

75. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes*	Review Date
New Policy	--	04/26/2017
Selected revision	Added Jadenu Sprinkle to drug target list and wherever appropriate in the policy. No criteria changes.	07/12/2017
Annual revision	No criteria changes	05/02/2018
Annual revision	No criteria changes	05/22/2019
Annual revision	Changed "prescribing physician" to "prescriber" where applicable. Added availability of generics to drug targets for Jadenu.	06/17/2020

PRIOR AUTHORIZATION POLICY

POLICY: Chelating Agents – Penicillamine Products

- Cuprimine® (penicillamine capsules – Valeant, generics)
- Depen® (penicillamine tablets – Meda, generics)

DATE REVIEWED: 04/15/2020

OVERVIEW

Penicillamine products ([Cuprimine® capsules, generics] and [Depen® tablets, generics]) are chelating agents indicated for the treatment of Wilson's disease.[1-2] These agents also have other indications for the treatment of cystinuria and treatment of patients with severe, active rheumatoid arthritis who have failed to respond to an adequate trial of conventional therapy. However, per product labeling, available evidence suggests that Cuprimine and Depen are not of value in ankylosing spondylitis. Product labeling for Cuprimine and Depen is identical, with the exception of the differences in dosage forms; Cuprimine is supplied as 250 mg capsules; Depen is supplied as 250 mg tablets.

Wilson's Disease Overview

Copper is an essential metal and is an important cofactor for many proteins.[4] However, normal dietary consumption and absorption of copper exceeds the amount that the body needs.[5] Copper homeostasis depends primarily on biliary excretion. Wilson's disease is an inherited disorder in which alterations in cellular copper processing and impaired biliary excretion lead to copper accumulation.[3-5] Copper initially builds up in the liver and eventually is released into the bloodstream and deposited into other organs (e.g., brain, kidneys, and cornea). The majority of patients with Wilson's disease are diagnosed between the ages of 5 and 35 years, with the most common presentations being liver disease, neurological disorder (e.g., tremor, ataxia, dystonia), or psychiatric illness.[4-5] The average prevalence of Wilson's disease is 30 cases per million individuals. Lifelong pharmacologic therapy is the mainstay of treatment for Wilson's disease;

without treatment, most patients will die from liver disease or progressive neurologic disease. Liver transplantation is reserved for severe or resistant cases. In patients with Wilson's disease, penicillamine acts as a general metal chelator and promotes urinary copper excretion.

Guidelines

The American Association for the Study of Liver Diseases (AASLD) provides guidelines for the diagnosis and management of Wilson's disease (2008).[4] It is noted that while the most experience in the treatment of this condition is with penicillamine; trientine hydrochloride capsules (Syprine, generics), another chelating agent, is also effective for the treatment of Wilson's disease, especially in patients who are intolerant of penicillamine or have clinical features indicating potential intolerance (history of renal disease of any sort, congestive splenomegaly causing severe thrombocytopenia, autoimmune tendency). The AASLD recommends that initial treatment for symptomatic patients include a chelating agent (penicillamine or trientine). For the treatment of presymptomatic patients or those on maintenance therapy, chelating agents and zinc are both treatment options. In pregnant patients, treatment for Wilson's disease should be continued due to the risk of liver failure with therapy interruption, but dosage reduction is advisable for penicillamine and trientine. Dose reductions with zinc are not necessary. Satisfactory outcomes have been shown with continuation of therapy with chelating agents (both penicillamine and trientine) during pregnancy. Liver transplantation should be considered in patients with acute liver failure due to Wilson's disease and in patients with decompensated cirrhosis unresponsive to chelation therapy.
The European Association for the Study of the Liver (EASL) also published a clinical practice guideline for the treatment of Wilson's disease (2012).[5] Like the AASLD, the EASL acknowledges that numerous studies have demonstrated the effectiveness of penicillamine. The EASL also notes that trientine has been shown to be an effective initial therapy. A chelating agent (penicillamine or trientine) is the recommended initial treatment of symptomatic patients, and again, a chelating agent or zinc may be used for the treatment of presymptomatic patients or patients established on maintenance therapy. In patients with neurological disease established on maintenance therapy either a chelating agent or zinc may be used; zinc may have a role as first-line therapy in these patients. If zinc is used, careful monitoring of transaminases is needed, with changing to chelators if these laboratory parameters are increasing. The EASL guidelines also state that despite teratogenicity concerns with penicillamine, treatment of Wilson's disease should be continued during pregnancy as the risks of withdrawing therapy outweigh those of continuing therapy. However, penicillamine and trientine dosage reductions are recommended in pregnant patients.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of the penicillamine products. All approvals are provided for the duration listed below. Because of the specialized skills required for evaluation and diagnosis of patients treated with penicillamine products as well as the monitoring required for adverse events and long-term efficacy, approval requires penicillamine products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of the penicillamine products is recommended in those who meet the following criteria:

I. Coverage of Cuprimine and penicillamine capsules are recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Wilson's Disease.** Approve for 3 years if the patient meets the following criteria (A, B, and C):
   - **A)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, or liver transplant physician; AND
   - **B)** The patient meets ONE of the following criteria (i, ii, iii, or iv):
     - **i.** The patient has tried Galzin® (zinc acetate capsules); OR
     - **ii.** The patient has tried another zinc product (e.g., zinc sulfate, zinc gluconate, zinc acetate); OR
     - **iii.** According to the prescriber, the patient has symptoms of Wilson's disease and zinc would not be an appropriate therapy; OR
     - **iv.** The patient has been started on therapy with a penicillamine product; AND
   - **C)** The patient meets one of the following (i or ii):
     - **i.** Generic penicillamine capsules are requested; OR
     - **ii.** If brand Cuprimine is prescribed, the patient has tried generic penicillamine capsules AND cannot take generic penicillamine capsules due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

2. **Cystinuria.** Approve for 3 years if the patient meets one of the following criteria (A or B):
   - **A)** Generic penicillamine capsules are requested; OR
   - **B)** If brand Cuprimine is prescribed, the patient has tried generic penicillamine capsules AND cannot take generic penicillamine capsules due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

3. **Rheumatoid Arthritis.** Approve for 3 years if the patient meets one of the following criteria (A or B):
   - **A)** Generic penicillamine capsules are requested; OR
   - **B)** If brand Cuprimine is prescribed, the patient has tried generic penicillamine capsules AND cannot take generic penicillamine capsules due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

II. Coverage of Depen and penicillamine tablets are recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Wilson's Disease.** Approve for 3 years if the patient meets the following criteria (A, B, and C):
   - **A)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, or liver transplant physician; AND
   - **B)** The patient meets ONE of the following criteria (i, ii, iii, or iv):
     - **i.** The patient has tried Galzin® (zinc acetate capsules); OR
     - **ii.** The patient has tried another zinc product (e.g., zinc sulfate, zinc gluconate, zinc acetate); OR
     - **iii.** According to the prescriber, the patient has symptoms of Wilson's disease and zinc would not be an appropriate therapy; OR
     - **iv.** The patient has been started on therapy with a penicillamine product.
   - **C)** The patient meets one of the following (i or ii):
     - **i.** Generic penicillamine tablets are requested; OR
     - **ii.** If brand Depen is prescribed, the patient has tried generic penicillamine tablets AND cannot take generic penicillamine tablets due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic

product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

2. **Cystinuria.** Approve for 3 years if the patient meets one of the following criteria (A or B):
   A) Generic penicillamine tablets are requested; OR
   B) If brand Depen is prescribed, the patient has tried generic penicillamine tablets AND cannot take generic penicillamine tablets due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

3. **Rheumatoid Arthritis.** Approve for 3 years if the patient meets one of the following criteria (A or B):
   A) Generic penicillamine tablets are requested; OR
   B) If brand Depen is prescribed, the patient has tried generic penicillamine tablets AND cannot take generic penicillamine tablets due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

The penicillamine products have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/11/2018
Annual revision	No criteria changes	04/07/2019
Annual revision	The Step Therapy component of the policy was removed. Addition of generic products was added. I. Coverage of Cuprimine was changed to coverage of Cuprimine and penicillamine capsules. **Wilson's Disease.** For the exception applying to patients having symptoms of Wilson's disease and zinc would not be an appropriate therapy, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). **Wilson's Disease, Cystinuria, & Rheumatoid Arthritis.** The criterion requiring the patient to try Depen was removed. Criteria requiring the generic penicillamine capsules be requested or the patient has tried generic penicillamine capsules AND cannot take generic penicillamine capsules due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction was added to the policy.II. Coverage of Depen was changed to coverage of Depen and penicillamine tablets. **Wilson's Disease.** For the exception applying to patients having symptoms of Wilson's disease and zinc would not be an appropriate therapy, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). **Wilson's Disease, Cystinuria, & Rheumatoid Arthritis.** Criteria requiring the generic penicillamine tablets be requested or the patient has tried generic penicillamine tablets AND cannot take generic penicillamine tablets due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction was added to the policy.	04/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Chelating Agents – Syprine Prior Authorization Policy

- Syprine® (trientine hydrochloride capsules – Valeant, generics)

REVIEW DATE: 09/23/2020

OVERVIEW

Trientine, a metal chelator, is indicated for the treatment of patients with Wilson's disease who are intolerant of penicillamine.[1] Trientine and penicillamine are not interchangeable; trientine should be used when treatment with penicillamine is no longer possible because of intolerable or life-endangering side effects. Trientine is not indicated for use in patients with cystinuria, rheumatoid arthritis, or biliary cirrhosis. In general, patients should remain under regular medical supervision while receiving trientine and patients (especially women) should be closely monitored for evidence of iron deficiency anemia. Controlled studies of trientine in pediatric patients are not available; however, it has been used in patients as young as 6 years with no adverse events. Other chelating agents indicated in the treatment of Wilson's disease include penicillamine capsules (Cuprimine®, generics) and Depen® (penicillamine tablets).[5-6] These agents also have other indications for the treatment of cystinuria and treatment of patients with severe, active rheumatoid arthritis who have failed to respond to an adequate trial of conventional therapy.

Disease Overview

Copper is an essential metal and is an important cofactor for many proteins.[3] However, normal dietary consumption and absorption of copper exceeds the amount that the body needs.[4] Copper homeostasis depends primarily on biliary excretion. Wilson's disease is an inherited disorder in which alterations in cellular copper processing and impaired biliary excretion lead to copper accumulation.[2-4] Copper initially builds up in the liver and eventually is released into

the bloodstream and deposited into other organs (e.g., brain, kidneys, and cornea). The majority of patients with Wilson's disease are diagnosed between the ages of 5 and 35 years, with the most common presentations being liver disease, neurological disorder (e.g., tremor, ataxia, dystonia), or psychiatric illness.[3-4] The average prevalence of Wilson's disease is 30 cases per million individuals. Lifelong pharmacologic therapy is the mainstay of treatment for Wilson's disease; without treatment, most patients will die from liver disease or progressive neurologic disease. Liver transplantation is reserved for severe or resistant cases. In patients with Wilson's disease, trientine acts as a general metal chelator and promotes urinary copper excretion.

Guidelines

The American Association for the Study of Liver Diseases (AASLD) provides guidelines for the diagnosis and management of Wilson's disease (2008).[3] It is noted that while the most experience in the treatment of this condition is with penicillamine, trientine is effective for the treatment of Wilson's disease, especially in patients who are intolerant of penicillamine or have clinical features indicating potential intolerance (history of renal disease of any sort, congestive splenomegaly causing severe thrombocytopenia, autoimmune tendency). Trientine has been found to be effective initial therapy, even in patients with decompensated liver disease at the outset. The AASLD recommends that initial treatment for symptomatic patients include a chelating agent (penicillamine or trientine). Neurological worsening following therapy initiation appears to be much less common with Syprine than with penicillamine. For the treatment of presymptomatic patients or those on maintenance therapy, chelating agents and zinc are both treatment options. Zinc appears preferable for presymptomatic children under the age of 3 years. In pregnant patients, treatment for Wilson's disease should be continued due to the risk of liver failure with therapy interruption, but dosage reduction is advisable for penicillamine and trientine. Satisfactory outcomes have been shown with continuation of therapy with chelating agents (both penicillamine and trientine) during pregnancy. Liver transplantation should be considered in patients with acute liver failure due to Wilson's disease and in patients with decompensated cirrhosis unresponsive to chelation therapy.

The European Association for the Study of the Liver (EASL) also published a clinical practice guideline for the treatment of Wilson's disease (2012).[4] Like the AASLD, the EASL acknowledges that numerous studies have demonstrated the effectiveness of penicillamine. The EASL also notes that trientine has been shown to be an effective initial therapy. A chelating agent (penicillamine or trientine) is the recommended initial treatment of symptomatic patients, and again, a chelating agent or zinc may be used for the treatment of presymptomatic patients or patients established on maintenance therapy. In patients with neurological disease established on maintenance therapy either a chelating agent or zinc may be used; zinc may have a role as first-line therapy in these patients. The EASL guidelines also state that despite teratogenicity concerns with penicillamine, treatment of Wilson's disease should be continued during pregnancy as the risks of withdrawing therapy outweigh those of continuing therapy. However, penicillamine and trientine dosage reductions are recommended in pregnant patients.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of trientine. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with trientine as well as the monitoring required for adverse events and long-term efficacy, approval requires trientine to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of trientine is recommended in those who meet the following criteria:

FDA-Approved Indications

4. Wilson's Disease. Approve for 3 years if the patient meets the following criteria (A and B):
- **D)** Patient meets ONE of the following criteria (i, ii, iii, iv, v or vi):
  - **i.** Patient has tried one penicillamine product and is intolerant to penicillamine therapy, according to the prescriber; OR

Note: Examples of penicillamine products are Cuprimine® (penicillamine capsules, generics), Depen® (penicillamine tablets, generics).

ii. Patient has clinical features indicating the potential for intolerance to penicillamine therapy, according to the prescriber; OR
Note: Specific clinical features include history of any renal disease, congestive splenomegaly causing severe thrombocytopenia, autoimmune tendency.

iii. Patient has a contraindication to penicillamine therapy, according to the prescriber; OR

iv. Patient has neurologic manifestations of Wilson's disease; OR

v. Patient is pregnant; OR

vi. Patient has been started on therapy with trientine (Syprine, generics).

E) The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, or liver transplant physician.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of trientine is not recommended in the following situations:

76. Biliary Cirrhosis. Trientine (Syprine, generics) is not indicated for the treatment of biliary cirrhosis.[1]

77. Cystinuria. Trientine (Syprine, generics) is not recommended for use in patients with cystinuria.[1] Unlike penicillamine, trientine does not contain a sulfhydryl moiety and therefore it is not capable of binding cysteine.

78. Rheumatoid Arthritis (RA). Trientine (Syprine, generics) is not recommended for use in patients with RA.[1] Per the prescribing information, trientine was not found to be effective in improving any clinical or biochemical parameter after 12 weeks of treatment of patients with RA.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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137. Depen® [prescribing information]. Somerset, NJ. Meda Pharmaceuticals Inc.; January 2019.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	09/12/2018
Annual Revision	**Wilson's Disease.** In reference to the criteria that the patient has tried one penicillamine product, wording was changed from "per the prescribing physician" to "according to the prescriber". In reference to the criteria that the patient has clinical features indicating the potential for intolerance to penicillamine therapy, wording was changed from "per the prescribing physician" to "according to the prescriber". In reference to the criteria that the patient has a contraindication to penicillamine therapy, wording was changed from "per the prescribing physician" to "according to the prescriber".	09/18/2019
Annual Revision	No criteria changes.	09/23/2020

PRIOR AUTHORIZATION POLICY

POLICY: Chenodal Prior Authorization Policy

- Chenodal™ (chenodiol tablets – Retrophin)

REVIEW DATE: 08/12/2020

OVERVIEW

Chenodal, a naturally occurring bile acid, is indicated for patients with radiolucent stones in well-opacifying gallbladders, in whom selective surgery would be undertaken except for the presence of increased surgical risk due to systemic disease or age.[1] The most widely used treatment for symptomatic gallstones is cholecystectomy.[2] Two naturally occurring bile acids are used in the treatment of gallstones: ursodeoxycholic acid (UrsoForte®, Urso-250®, [ursodiol tablets, generics], Actigall® [ursodiol capsules, generics]) and chenodeoxycholic acid/chenodiol (Chenodal).[3] These agents reduce biliary cholesterol; however, their exact mechanisms differ. Both Chenodal and ursodiol promote the gradual dissolution of radiolucent gallstones over a period of 6 months to 2 years.[2]

Cerebrotendinous xanthomatosis (CTX) is a lipid storage disorder with various clinical manifestations including juvenile cataracts, tendon xanthomas, premature atherosclerosis, and progressive neurologic disturbance (e.g., ataxia, seizures, psychiatric disorders, and peripheral neuropathy).[4] Other conditions associated with CTX include osteoarthritis, skeletal fractures, pulmonary insufficiency, renal and hepatic calculi, and childhood chronic diarrhea. CTX is the result of a mutated enzyme (cytochrome P450 27-sterol hydroxylase [CYP27]) which is normally responsible for the conversion of cholesterol to cholic acid and chenodeoxycholic acid. In CTX, reduced synthesis of cholic- and chenodeoxycholic acids seem to result in failed feedback inhibition of cholesterol production, in turn leading to hallmark laboratory findings of the disorder: increased serum cholestanol concentrations and elevated urinary bile alcohols.[5] Replacement therapy with chenodiol inhibits abnormal bile acid synthesis and is most effective in reducing elevated plasma cholesterol concentrations and eliminating bile alcohols.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Chenodal. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Chenodal as well as the monitoring required for adverse events and long-term efficacy, approval requires Chenodal to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Chenodal is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Gallstones.** Approve for 3 years if the patient meets one of the following criteria (A or B):
   A) Patient has tried an ursodiol product; OR
   B) Patient is currently receiving an ursodiol product.

Other Uses with Supportive Evidence

2. Cerebrotendinous Xanthomatosis. Approve for 3 years if Chenodal is prescribed by or in consultation with a metabolic specialist who treats patients with cerebrotendinous xanthomatosis or a specialist who focuses in the treatment of cerebrotendinous xanthomatosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Chenodal is not recommended in the following situations:

7. **Combination Therapy with Cholbam™** (cholic acid capsules). There are no efficacy data available to support use of combination therapy with Chenodal and Cholbam.

8. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	07/11/2018
Annual Revision	No criteria changes.	07/17/2019
Annual Revision	No criteria changes.	08/12/2020

PRIOR AUTHORIZATION POLICY

POLICY: Cholbam® (cholic acid capsules – Retrophin)

DATE REVIEWED: 06/03/2020

OVERVIEW

Cholbam, a bile acid, is indicated for the treatment of bile acid synthesis disorders due to single enzyme defects (SEDs).[1] It is also indicated for adjunctive treatment of peroxisomal disorders (PDs), including Zellweger spectrum disorders, in patients who exhibit manifestations of liver disease, steatorrhea, or complications from decreased fat soluble vitamin absorption. The effects of Cholbam on extrahepatic manifestations (e.g., neurologic symptoms) of bile acid synthesis disorders due to SEDs or PDs have not been established.

The prescribing information states that treatment with Cholbam should be discontinued if liver function does not improve within 3 months of the start of treatment or if complete biliary obstruction develops.[1]

Bile Acid Synthesis Disorders

Bile acids are found in the liver and have several biological roles, including promotion of bile flow and intestinal absorption of fat and fat soluble vitamins.[2,3] The two primary bile acids are cholic acid and chenodeoxycholic acid (available as Chenodal® [chenodiol tablets]). Bile acids are formed from cholesterol; inadequate bile acid production leads to accumulation of cholesterol in the body, as well as other intermediary metabolites. This can result in damage to various organ systems. Severe cases may progress to cirrhosis and liver failure. Progressive neurologic disease may also occur, even in the absence of liver disease. There are at least 17 known enzymes involved in bile acid synthesis.[3] Primary bile acid synthesis disorders may be caused by a defect in the gene encoding any one of these enzymes, and therefore these conditions are also termed SEDs.[2,3] The estimated incidence of bile acid synthesis disorders due to SEDs is 1 to 9 per one million live births.[4] The most common of all of the bile acid SEDs is 3β-hydroxy-C_{27}-steroid oxidoreductase deficiency (3β-HSD gene defect).[5] Other common defects include Δ^4-3-oxosteroid 5β-reductase deficiency (aldo-keto reductase 1D1 [AKR1D1] gene), 27-hydroxylase deficiency (cerebrotendinous xanthomatosis [CTX]), and alpha-methylacyl-CoA racemase deficiency (AMACR gene). Cholbam is indicated for all SEDs, though the majority of patients in the pivotal study for Cholbam had 3β-HSD defect.[1] Chenodal has been used for CTX though it is not labeled for this condition.[6] Bile acid synthesis disorders may be diagnosed with either genetic testing or urine bile acid profile by Fast Atom Bombardment ionization – mass spectrometry (FAB-MS).[10] FAB-MS was used for diagnosis in the pivotal trial; gene sequencing was not available when the trial was conducted.[11] However, gene sequencing is now available for many of the affected enzymes.

Peroxisomal Disorders (PDs)

PDs occur due to genetic mutations which are essential to the proper formation of peroxisomes.[7] Peroxisomes are found throughout the body but are most numerous in the kidneys and liver.[7,8] Among their many roles, peroxisomes are vital to the production of bile acids, as well as plasmalogens, which are important for neurologic function.[8] Peroxisomal disorders are estimated to affect approximately 1 in 50,000 live births.[4] Zellweger spectrum disorder is a type of PD and includes Zellweger syndrome, neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease. Zellweger syndrome is the most severe form in the spectrum, followed by NALD, and infantile Refsum disease is the least severe form. Cholbam is indicated only for adjunctive treatment of liver disease symptoms such as steatorrhea. Patients with Zellweger spectrum disorders present with other primary clinical issues such as feeding problems in infants, weak muscle tone, hearing and vision loss, and seizures. Liver involvement with Zellweger spectrum disorders may be diagnosed by genetic testing or by bile acid profile testing with mass spectrometry.[12] FAB-MS was used for diagnosis in the pivotal trial; gene sequencing was not available when the trial was conducted.[11] However, gene sequencing is now available for many of the affected enzymes.

GUIDELINES

A joint guideline by the North American and European societies for Pediatric Gastroenterology, Hepatology, and Nutrition is available (2017).[9] The guideline, which briefly addresses evaluation of cholestatic jaundice in infants, provides recommendations for diagnosis of bile acid synthesis disorders. It is possible to perform rapid diagnosis of potential inborn errors in bile acid synthesis from urinary bile acid analysis; fast atom bombardment mass spectrometry of urine is recommended. The guideline also notes that molecular techniques identify the specific mutations in genes encoding enzymes responsible for bile acid synthesis.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Cholbam. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cholbam as well as the monitoring required for efficacy, approval requires Cholbam to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 1 year in duration unless otherwise noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cholbam is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Bile Acid Synthesis Disorders Due to Single Enzyme Defects (SEDs).** Approve for the duration noted if the patient meets one of the following conditions (A or B):
   - **A)** Initial Therapy: Approve for 3 months if the patients meets both of the following criteria (i and ii):
     - **i.** Patient has a diagnosis of SED based on at least one of the following criteria (a or b):
       - **a)** An abnormal urinary bile acid as confirmed by Fast Atom Bombardment ionization – Mass Spectrometry (FAB-MS) analysis; OR
       - **b)** Molecular genetic testing consistent with the diagnosis; AND
     - **ii.** Cholbam is prescribed by or in consultation with a hepatologist, metabolic specialist, or a gastroenterologist.
   - **B)** Patients Currently Receiving Cholbam: Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient has responded to initial Cholbam therapy with an improvement in liver function tests (e.g., aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin levels); AND
     - **ii.** Patient does not have complete biliary obstruction; AND
     - **iii.** Cholbam is prescribed by or in consultation with a hepatologist, metabolic specialist, or a gastroenterologist.

2. **Bile Acid Synthesis Disorders Due to Peroxisomal Disorders (PDs), Including Zellweger Spectrum Disorders.** Approve for the duration noted if the patient meets one of the following conditions (A or B):
   - **A)** Initial Therapy: Approve for 3 months if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient has peroxisomal disorders with at least one of the following criteria (a or b):
       - **a)** An abnormal urinary bile acid analysis by Fast Atom Bombardment ionization – Mass Spectrometry (FAB-MS); OR
       - **b)** Molecular genetic testing consistent with the diagnosis; AND
     - **ii.** Patient has liver disease, steatorrhea, or complications from decreased fat soluble vitamin absorption (e.g., rickets); AND
     - **iii.** Cholbam is prescribed by or in consultation with a hepatologist, metabolic specialist, or a gastroenterologist.
   - **B)** Patients Currently Receiving Cholbam: Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient has responded to initial Cholbam therapy as per the prescribing physician (e.g., improvements in liver enzymes, improvement in steatorrhea); AND

ii. Patient does not have complete biliary obstruction; AND
iii. Cholbam is prescribed by or in consultation with a hepatologist, metabolic specialist, or a gastroenterologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Cholbam has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

79. Combination Therapy with Chenodal. There are no efficacy data available to support use of combination therapy with Cholbam and Chenodal.

80. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual revision	No criteria changes	05/02/2018
Annual revision	**Bile Acid Synthesis Disorders Due to Single Enzyme Defects (SEDs):** Added molecular genetic testing as an option for a test that confirms the diagnosis for initial therapy. **Bile Acid Synthesis Disorders Due to Peroxisomal Disorders (PDs), Including Zellweger Spectrum Disorders:** Added molecular genetic testing as an option for a test that confirms the diagnosis for initial therapy.	05/22/2019
Annual revision	No criteria changes.	06/03/2020

PRIOR AUTHORIZATION POLICY

POLICY: Cinacalcet (Sensipar) Prior Authorization Policy
- Sensipar® (cinacalcet tablets – Amgen, generic)

REVIEW DATE: 02/10/2021

Overview
Cinacalcet (Sensipar, generic), a calcium-sensing receptor agonist (calcimimetic), is indicated for the following uses:[1]
- **Hypercalcemia** in adult patients with **parathyroid carcinoma**.
- **Hypercalcemia** in adult patients with **primary hyperparathyroidism** for whom parathyroidectomy would be indicated on the basis of serum calcium levels, but who are unable to undergo parathyroidectomy.
- **Secondary hyperparathyroidism** in adult patients with chronic kidney disease (CKD) on dialysis.

Disease Overview
Secondary hyperparathyroidism is a frequent complication of CKD caused by a reduction in circulating calcitriol levels and disturbances in calcium and phosphorous metabolism.[2] This leads to increases in the parathyroid hormone (PTH) levels, which then leads to osteoclastic activity resulting in bone resorption and marrow fibrosis.

Parathyroid carcinoma is a rare malignant cancer and is an uncommon cause of primary hyperparathyroidism.[3] The condition is associated with higher serum calcium and PTH levels than primary hyperparathyroidism due to benign adenoma. The primary cause of morbidity in patients with parathyroid carcinoma is due to complications of hypercalcemia (e.g., cardiac arrhythmias, renal failure). Surgical resection of the malignancy may relieve symptoms and reduce serum calcium levels. Medical therapy with cinacalcet and intravenous bisphosphonates are useful adjunct therapies to control hypercalcemia.

Guidelines
The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines (2017) for the treatment of CKD-mineral bone disorder (MBD) recommend the use of cinacalcet, calcitriol, vitamin D analogues, or a combination of these agents in CKD stage 5D (dialysis) patients with elevated or rising PTH levels.[4] The guidelines recognize that there are no randomized controlled trials showing that treatment to achieve a specific PTH level results in improved outcomes. There is no established "cause and effect" relationship between the measured biochemical variables and observed outcomes. Therefore, the guidelines recommend interpreting changes in PTH in conjunction with calcium and phosphorous levels to guide therapeutic decisions. In general, in patients with CKD stage 5D, the KDIGO guidelines suggest maintaining intact PTH (iPTH) levels in the range of approximately two to nine times the upper limit of normal for the assay. Changes in therapy are suggested if there are marked changes in PTH levels in either direction within this range. If iPTH levels fall below two times the upper limit of normal for the assay, the use of calcimimetics, calcitriol, or vitamin D analogues should be reduced or discontinued.

Other Uses with Supportive Evidence
The KDIGO clinical practice guidelines (2017) for the treatment of CKD-MBD note that although cinacalcet is not approved for the treatment of hyperparathyroidism in kidney transplant recipients, it is used in these patients, especially those with significant hypercalcemia.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of cinacalcet. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with cinacalcet as well as the monitoring required for adverse events and long-term efficacy, approval requires cinacalcet to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: When available, the ICD-9/ICD-10 codes for Malignant Neoplasm of Parathyroid Gland (ICD-9: 194.1* and ICD-10: C75.0*) AND "oncologist or endocrinologist" will be used as part of automation to allow approval of the requested medication.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of cinacalcet is recommended in those who meet the following criteria:

FDA-Approved Indications

21. Hypercalcemia due to Parathyroid Carcinoma. Approve for 1 year if cinacalcet is prescribed by or in consultation with an oncologist or endocrinologist.

22. Hypercalcemia in Patients with Primary Hyperparathyroidism. Approve for 1 year if the patient meets both of the following criteria (A and B):
- **A)** Patient has failed or is unable to undergo a parathyroidectomy due to a contraindication; AND
- **B)** The medication is prescribed by or in consultation with a nephrologist or endocrinologist.

23. Secondary Hyperparathyroidism. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient has chronic kidney disease and is on dialysis; AND
- **B)** The baseline (prior to starting cinacalcet therapy) intact parathyroid hormone (iPTH) level is at least two times the upper limit of normal as defined by the laboratory reference value measured on two separate occasions; AND
- **C)** The medication is prescribed by or in consultation with a nephrologist or endocrinologist.

Other Uses with Supportive Evidence

24. Hyperparathyroidism in Post-Renal Transplant Patients. Approve for 1 year if the patient meets both of the following conditions (A and B):
- **A)** The baseline (prior to starting cinacalcet therapy) calcium and intact parathyroid hormone (iPTH) levels are above the normal range, as defined by the laboratory reference values; AND
- **B)** The medication is prescribed by or in consultation with a transplant physician, nephrologist, or endocrinologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of cinacalcet is not recommended in the following situations:

81. Patients with Primary Hyperparathyroidism eligible for Parathyroidectomy. Parathyroidectomy is the primary treatment for primary hyperparathyroidism.

82. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes	02/06/2019
Annual Revision	No criteria changes	02/12/2020
Selected Revision	• **Secondary Hyperparathyroidism:** Added "baseline" to criterion regarding intact parathyroid hormone level to read: The baseline (prior to starting cinacalcet therapy) intact parathyroid hormone (iPTH) level is at least two times the upper limit of normal as defined by the laboratory reference value measured on two separate occasions". • **Hyperparathyroidism in Post-Renal Transplant Patients:** Consolidated the Initial and Continuation Criteria set. Approval is based on two criteria: The baseline (prior to starting cinacalcet therapy) calcium and intact parathyroid hormone (iPTH) levels are above the normal range as defined by the laboratory reference values and Cinacalcet is prescribed by, or in consultation with a transplant physician, nephrologist, or endocrinologist.	03/11/2020
Annual Revision	No criteria changes.	02/10/2021

PRIOR AUTHORIZATION POLICY

POLICY: Colony Stimulating Factors – Filgrastim Products Prior Authorization Policy

- Neupogen® (filgrastim injection for subcutaneous or intravenous use – Amgen)
- Nivestym™ (filgrastim injection for subcutaneous or intravenous use – Hospira/Pfizer)
- Zarxio® (filgrastim-sndz injection for subcutaneous or intravenous use – Sandoz)

REVIEW DATE: 08/19/2020

OVERVIEW

Filgrastim products leukocyte growth factors, are indicated for the following uses:[1-3]

- **Decrease the incidence of infection as manifested by febrile neutropenia**, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.
- **Mobilization of hematopoietic progenitor cells,** into the peripheral blood for collection by leukapheresis.
- **Reduce the time to neutrophil recovery and the duration of fever,** following induction or consolidation chemotherapy treatment of adults with acute myeloid leukemia (AML).
- **Reduce the duration of neutropenia and neutropenia-related clinical sequelae (e.g., febrile neutropenia),** in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation.
- **Reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers),** in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

Nivestym and Zarxio are two products that are biosimilars to Neupogen.[2,3] Neupogen is the only agent indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).[1] Granix (tbo-filgrastim injection for subcutaneous use) is another filgrastim product.[4]

Guidelines

The National Comprehensive Cancer Network (NCCN) address the use of filgrastim products in several guidelines.

- **Acute Lymphoblastic Leukemia:** Guidelines (version 2.2020 – January 15, 2020) recommend granulocyte colony-stimulating factors (CSFs) as supportive care for myelosuppressive blocks of therapy or as directed by treatment protocol.[7]
- **Hematopoietic Growth Factors:** Guidelines (version 2.2020 – January 27, 2020) recommend filgrastim, along with other CSFs, for prophylactic use if the patient is receiving anti-cancer medications that are associated with a high (> 20%) incidence of severe neutropenia with fever.[5] Consider CSF therapy for patients with an intermediate (10% to 20%) probability of developing febrile neutropenia based on risk factors. The NCCN guidelines also recommend therapy with a CSFs in other scenarios in those given myelosuppressive chemotherapy. Filgrastim products are also recommended for mobilization and following hematopoietic cell transplant.
- **Management of Immunotherapy-Related Toxicities:** Guidelines (version 1.2020 – December 16, 2019) recommend granulocyte CSFs as supportive care for neutropenic patients with Grade 1 cytokine release syndrome resulting from chimeric antigen receptor (CAR) T-cell therapy.[20]
- **Myelodysplastic Syndromes (MDS):** Guidelines (version 2.2020 – February 28, 2020) recommend filgrastim for use in certain patients with MDS (e.g., neutropenic patients with recurrent or resistant infections, combination use with epoetin alfa or Aranesp® [darbepoetin alfa injection] in patients with anemia]).[6]

The American Society of Clinical Oncology clinical practice guidelines for the use of white blood cell growth factors (2015) recommends CSFs to reduce the risk of febrile neutropenia in patients receiving cancer chemotherapy.[6] CSFs may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected. The guidelines state CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum.

Other Uses With Supportive Evidence

Neutropenia occurs in patients with HIV and may be caused by medications or due to the disease process. Studies have demonstrated positive outcomes with the use of filgrastim for the treatment of neutropenia in this patient population.[9-12]

Filgrastim has been used for agranulocytosis caused by non-cytotoxic medications, primarily described in case series, case reports and literature reviews.[13-19]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of filgrastim products. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with filgrastim products as well as the monitoring required for adverse events and long-term efficacy, approval for some conditions requires filgrastim products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of filgrastim products is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Cancer in a Patient Receiving Myelosuppressive Chemotherapy.** Approve for 6 months if the patient meets the following (A and B):
   A) Patient meets ONE of the following conditions (i, ii, iii, or iv):
      iii. Patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk is at least 20% based on the chemotherapy regimen); OR
      iv. Patient is receiving myelosuppressive anti-cancer medications that are associated with a risk of febrile neutropenia, but the risk is less than 20% based on the chemotherapy regimen and the patient has at least one risk factor for febrile neutropenia according to the prescriber.
      Note: Examples of risk factors include age ≥ 65 years; prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver and/or renal dysfunction; poor performance status; or human immunodeficiency virus (HIV) infection; OR
      v. Patient has had a neutropenic complication from prior chemotherapy and did not receive prophylaxis with a colony stimulating factor and a reduced dose or frequency of chemotherapy may compromise treatment outcome; OR
      Note: Examples of colony-stimulating factors include filgrastim products, pegfilgrastim products, and sargramostim products (e.g., Leukine®).
      vi. Patient who has received chemotherapy has febrile neutropenia and has at least one risk factor for poor clinical outcomes or for developing infection-associated complications according to the prescriber; AND
      Note: Examples of risk factors include sepsis syndrome; age > 65 years; severe neutropenia (absolute neutrophil count [ANC] < 100 cells/mm^3); neutropenia expected to be > 10 days in duration; invasive fungal infection; or other clinically documented infections.
   B) The agent is prescribed by, or in consultation with, an oncologist or hematologist.

2. **Acute Myeloid Leukemia in a Patient Receiving Chemotherapy.** Approve for 6 months if prescribed by or in consultation with an oncologist or hematologist.

3. **Bone Marrow Transplant in a Patient with Cancer Who Received Chemotherapy.** Approve for 1 month if prescribed by or in consultation with a hematologist, an oncologist, or a physician who specializes in transplantation.

4. **Peripheral Blood Progenitor Cell Collection and Therapy.** Approve for 1 month if prescribed by or in consultation with an oncologist, a hematologist or a physician who specializes in transplantation.

5. **Severe Chronic Neutropenia (e.g., Congenital Neutropenia, Cyclic Neutropenia, Idiopathic Neutropenia).** Approve for 6 months if prescribed by or in consultation with a hematologist.

6. **Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome).** Approve for 1 month if prescribed by or in consultation with a physician who has expertise in treating acute radiation syndrome.

Other Uses with Supportive Evidence

7. **Neutropenia Associated with Human Immunodeficiency Virus (HIV) or Acquired Immunodeficiency Syndrome (AIDS).** Approve for 4 months if the agent is prescribed by or in consultation with a physician that specializes in infectious diseases, a hematologist, or a physician who specializes in the management of HIV/AIDS.

8. **Myelodysplastic Syndromes.** Approve for 3 months if prescribed by, or in consultation with, an oncologist or hematologist.

9. **Drug-Induced (Non-Chemotherapy) Agranulocytosis or Neutropenia.** Approve for 1 month.

10. **Acute Lymphoblastic Leukemia.** Approve for 1 month if prescribed by or in consultation with an oncologist or a hematologist.

11. **Radiation-Induced Neutropenia.** Approve for 6 months if the patient meets the following criteria (A and B):

A) Patient is not currently receiving chemotherapy; AND
B) The agent is prescribed by, or in consultation with, an oncologist, radiologist or radiation oncologist.

12. Cytokine Release Syndrome Associated with Chimeric Antigen Receptor (CAR) T-Cell Therapy. Approve for 1 month if prescribed for a patient who has neutropenia.
Note: Examples of CAR T-cell therapy include Kymriah™ (tisagenlecleucel intravenous suspension) and Yescarta™ (axicabtagene ciloleucel intravenous suspension).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of filgrastim products is not recommended in the following situations:

9. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Neupogen® injection for subcutaneous or intravenous use [prescribing information]. Thousand Oaks, CA: Amgen, Inc.; June 2018.
2. Zarxio™ injection for subcutaneous or intravenous use [prescribing information]. Princeton, NJ: Sandoz; August 2019.
3. Nivestym™ injection for subcutaneous or intravenous use [prescribing information]. Lake Forest, IL and New York, NY: Hospira and Pfizer; July 2018.
4. Granix® injection for subcutaneous use [prescribing information]. North Wales, PA: Teva Pharmaceuticals; March 2019.
5. The NCCN Hematopoietic Growth Factors Clinical Practice Guidelines in Oncology (version 2.2020 – January 27, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 22, 2020.
6. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 2.2020 – February 28, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed: July 22, 2020.
7. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 2.2020 – January 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at http://www.nccn.org. Accessed on July 22, 2020.
8. Smith TJ, Bohlke K, Lyman GH, Carson KR, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2015;33(28):3199-3212.
9. Kuritzkes DR, Parenti D, Ward DJ, et al, and the G-CSF 930101 study group. Filgrastim prevents severe neutropenia and reduces infective morbidity in patients with advanced HIV infection: results of a randomized, multicenter controlled trial. *AIDS*. 1998;12:65-71.
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11. Kurizkes DR. Neutropenia, neutrophil dysfunction, and bacterial infection in patients with human immunodeficiency virus disease: the role of granulocyte colony-stimulating factor. *Clin Infect Dis*. 2000;30:256-260.
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13. Tesfa D, Keisu M, Palblad J. Idiosyncratic drug-induced agranulocytosis: possible mechanism and management. *Am J Hematol*. 2009;84:428-434.
14. Andersohn F, Konzen C, Garbe E. Systematic review: Agranulocytosis induced by nonchemotherapy drugs. *Ann Intern Med*. 2007;146:657-665.
15. Beaushesne MF, Shalansky SJ. Nonchemotherapy drug-induced agranulocytosis: a review of 118 patients treated with colony-stimulating factors. *Pharmacother*. 1999;19(3):299-305.
16. Bhatt V, Saleem A. Review: Drug-induced neutropenia-pathophysiology, clinical features, and management. *Ann Clin Lab Sci*. 2004;34(2):131-136.
17. Curtis BR. Drug-induced immune neutropenia/agranulocytosis. *Immunohematology*. 2014;30(2):95-101.
18. Andres E, Mourot-Cottet R. Non-chemotherapy drug-induced neutropenia – an update. *Expert Opin Drug Saf*. 2017;16(11):1235-1242.
19. Andres E, Mourot-Cottet R, Maloisel F, et al. Idiosyncratic drug-induced neutropenia and agranulocytosis. *QJM*. 2017 Jan 9. [Epub ahead of print].
20. The NCCN Management of Immunotherapy-Related Toxicities Clinical Practice Guidelines in Oncology (version 1.2020 – December 16, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 22, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date

Annual Revision	The name of the policy was changed from Colony Stimulating Factors – Neupogen PA to Colony Stimulating Factors – Filgrastim products PA. This includes the filgrastim biosimilars of Zarxio and Nivestym. Nivestym was just added to the policy. Zarxio was added to the policy as well and the individual PA policy for Zarxio was retired. Criteria that stated Neupogen or Zarxio was changed to state filgrastim to address all products. For the criteria regarding patients with cancer receiving myelosuppressive therapy in the criteria that reference a colony stimulating factor, the terminology of filgrastim and pegfilgrastim products were added, along with the listing of the individual products, which included adding Nivestym and Fulphila.	08/01/2018
Selected Revision	For the indication regarding Patients with Cancer (Adults and Children) Receiving Myelosuppressive Chemotherapy, removed "(adults and children)".	08/08/2018
Annual Revision	The following changes per the specific indications are cited below: **1. Cancer in Patients Receiving Myelosuppressive Chemotherapy:** CSFs are provided as examples in a Note rather than as part of the criterion. Also, risk factors are now listed as Notes rather than as part of the criterion. The wording in reference to according to the "according to the prescribing physician" was changed to "according to the prescriber". **2. Acute Myeloid Leukemia in Patients Receiving Chemotherapy:** The qualifier of "adults" was removed from the indication. **3. Peripheral Blood Progenitor Cell Collection and Therapy:** The qualifier of "adults and children" was removed from the indication. **4. Severe Chronic Neutropenia:** The qualifier of "adults and children" was removed from the indication. **5. Neutropenia Associated with HIV or AIDS:** The qualifier of "adults" was removed from the indication. **6. MDS:** The qualifier of "adults" was removed from the indication. **7. Aplastic Anemia:** The criteria for approval were eliminated for this condition.	08/21/2019
Annual Revision	Cytokine release syndrome associated with chimeric antigen receptor (CAR) T-cell therapy and criteria were added as an approval condition.	08/19/2020

PRIOR AUTHORIZATION POLICY

POLICY: Colony Stimulating Factors – Granix Prior Authorization Policy

- Granix® (tbo-filgrastim injection for subcutaneous use – Teva)

REVIEW DATE: 08/19/2020

OVERVIEW

Granix, a leukocyte growth factor, is indicated to reduce the duration of severe neutropenia in adults and pediatric patients 1 month of age and older with non-myeloid malignancies receiving myelosuppressive anti-cancer medications associated with a clinically significant incidence of febrile neutropenia.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) address the use of Granix in guidelines.

- **Hematopoietic Growth Factors:** Guidelines (version 2.2020 – January 27, 2020) recommend Granix, along with other granulocyte colony stimulating factors (CSFs), for prophylactic use if the patient is receiving anti-cancer medications that are associated with a high (> 20%) incidence of severe neutropenia with fever.[2] Consider CSF therapy for patients with an intermediate (10% to 20%) probability of developing febrile neutropenia based on risk factors. The NCCN guidelines also recommend therapy with a CSFs in other scenarios in those given myelosuppressive chemotherapy. Granix is also recommended for mobilization and following hematopoietic cell transplant.
- **Myelodysplastic Syndromes (MDS):** Guidelines (version 2.2020 – February 28, 2020) recommend Granix for use in certain patients with MDS (e.g., neutropenic patients with recurrent

or resistant infections, combination use with epoetin alfa or Aranesp® [darbepoetin alfa injection] in patients with anemia]).[3]

The American Society of Clinical Oncology clinical practice guidelines for the use of white blood cell growth factors (2015) recommends CSFs to reduce the risk of febrile neutropenia in patients receiving cancer chemotherapy.[4] CSFs may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected. The guidelines state CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Granix. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Granix as well as the monitoring required for adverse events and long-term efficacy, approval requires Granix to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Granix is recommended in those who meet the following criteria:

FDA-Approved Indications

12. Cancer in a Patient Receiving Myelosuppressive Chemotherapy. Approve for 6 months if the patient meets the following (A and B):

B) Patient meets ONE of the following conditions (i, ii, iii, or iv):

vii. Patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk is at least 20% based on the chemotherapy regimen); OR

viii. Patient is receiving myelosuppressive anti-cancer medications that are associated with a risk of febrile neutropenia, but the risk is less than 20% based on the chemotherapy regimen and the patient has at least one risk factor for febrile neutropenia according to the prescriber; OR

Note: Examples of risk factors include age ≥ 65 years; prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver and/or renal dysfunction; poor performance status; or human immunodeficiency virus (HIV) infection.

ix. Patient has had a neutropenic complication from prior chemotherapy and did not receive prophylaxis with a colony stimulating factor and a reduced dose or frequency of chemotherapy may compromise treatment outcome; OR

Note: Examples of colony-stimulating factors include filgrastim products, pegfilgrastim products, and sargramostim products (e.g., Leukine®).

x. Patient who has received chemotherapy has febrile neutropenia and has at least one risk factor for poor clinical outcomes or for developing infection-associated complications according to the prescriber; AND

Note: Examples of risk factors include sepsis syndrome; age > 65 years; severe neutropenia (absolute neutrophil count [ANC] < 100 cells/mm^3); neutropenia expected to be > 10 days in duration; invasive fungal infection; other clinically documented infections; or prior episode of febrile neutropenia.

B) The medication is prescribed by, or in consultation with, an oncologist or hematologist.

Other Uses with Supportive Evidence

13. Peripheral Blood Progenitor Cell Collection and Therapy. Approve for 1 month if prescribed by or in consultation with an oncologist, a hematologist or a physician who specializes in transplantation.

14. Myelodysplastic Syndromes. Approve for 3 months if prescribed by, or in consultation with, an oncologist or hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Granix is not recommended in the following situations:

10. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

21. Granix® injection [prescribing information]. North Wales, PA: Teva Pharmaceuticals; March 2019.
22. The NCCN Hematopoietic Growth Factors Clinical Practice Guidelines in Oncology (version 2.2020 – January 27, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 22, 2020.
23. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 2.2020 – February 28, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed: July 22, 2020.
24. Smith TJ, Bohlke K, Lyman GH, Carson KR, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2015;33(28):3199-3212.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	For the criteria regarding patients with cancer receiving myelosuppressive therapy who are adults, in the criteria that reference a colony stimulating factor, the terminology of filgrastim and pegfilgrastim products were added, along with the listing of the individual products, which included adding Nivestym and Fulphila.	08/01/2018
Selected Revision	For the indication of cancer patients receiving myelosuppressive chemotherapy, removed the notation "who are adults" to reflect FDA-approval of Granix in children.	08/08/2018
Annual Revision	The following changes per the specific indications are cited below: **8. Cancer in Patients Receiving Myelosuppressive Chemotherapy:** CSFs are now provided as examples in a Note rather than as part of the criterion. Also, risk factors are now listed as Notes rather than as part of the criterion. The wording in reference to "according to the prescribing physician" was changed to "according to the prescriber". **9. Peripheral Blood Progenitor Cell Collection and Therapy:** The qualifier of "adults and children" was removed from the indication.	08/21/2019
Annual Revision	Myelodysplastic Syndromes and criteria were added as an approval condition.	08/19/2020

PRIOR AUTHORIZATION POLICY

POLICY: Colony Stimulating Factors – Leukine Prior Authorization Policy

- Leukine® (sargramostim injection – Partner Therapeutics)

REVIEW DATE: 08/19/2020

OVERVIEW

Leukine, a recombinant human granulocyte macrophage colony stimulating factor (GM-CSF), is indicated for the following uses:[1]

- **Acute exposure to myelosuppressive doses of radiation,** to increase survival in adult and pediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation (hematopoietic syndrome of acute radiation syndrome).
- **Acute myeloid leukemia following induction chemotherapy**, to shorten the time to neutrophil recovery and to reduce the incidence of severe, life-threatening, or fatal infections in patients ≥ 55 years of age.
- **Allogeneic bone marrow transplantation,** for acceleration of myeloid reconstitution in adult and pediatric patients ≥ 2 years of age undergoing allogeneic bone marrow transplantation from human leukocyte antigen-matched related donors.
- **Allogeneic or autologous bone marrow transplantation: treatment of delayed neutrophil recovery or graft failure,** treatment of patients ≥ 2 years of age who have undergone allogeneic or autologous bone marrow transplantation in whom neutrophil recovery is delayed or failed.
- **Autologous peripheral blood progenitor cell (PBPC) and bone marrow transplantation,** acceleration of myeloid reconstitution after autologous PBPC or bone marrow transplantation in

adult and pediatric patients 2 years of age and older with non-Hodgkin's lymphoma, acute lymphoblastic leukemia, and Hodgkin's lymphoma.

- **Autologous peripheral blood progenitor cell mobilization and collection,** in adult patients with cancer undergoing autologous hematopoietic stem cell transplantation for the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis.

Other Uses With Supportive Evidence

Unituxin® (dinutuximab injection for intravenous use) is indicated for use in combination with GM-CSF, interleukin-2, and 13-cis-retinoic acid for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to first-line, multiagent, multimodality therapy.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Leukine. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Leukine as well as the monitoring required for adverse events and long-term efficacy, approval requires Leukine to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Leukine is recommended in those who meet the following criteria:

FDA-Approved Indications

7. **Acute Myeloid Leukemia.** Approve for 6 months if the patient is prescribed by or in consultation with an oncologist or a hematologist.

8. **Peripheral Blood Progenitor Cell Collection and Therapy.** Approve for up to 14 days if the agent is prescribed by or in consultation with an oncologist, a hematologist, or a physician that specializes in transplantation.

9. **Bone Marrow Transplant.** Approve for 1 month if prescribed by or in consultation with a hematologist, an oncologist, or a physician who specializes in transplantation.

10. **Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome).** Approve for 1 month if the agent is prescribed by or in consultation with a physician with expertise in treating acute radiation syndrome.

Other Uses with Supportive Evidence

11. **Neuroblastoma.** Approve for 6 months if the patient meets the following criteria (A, B and C):
    - **A)** The patient is < 18 years of age; AND
    - **B)** The patient is receiving Leukine in a regimen with Unituxin® (dinutuximab injection for intravenous use); AND
    - **C)** The agent is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Leukine is not recommended in the following situations:

11. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

28. Leukine® injection for intravenous or subcutaneous use [prescribing information]. Lexington, MA: Partner Therapeutics; May 2018.
29. Unituxin™ injection for intravenous use [prescribing information]. Silver Springs, MD: United Therapeutic Corporation; March 2017.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	03/13/2019
Early annual revision	Changes per the specific indications were as follows: 1. **Bone Marrow Transplant.** Criteria were added that approves Leukine for 1 month if prescribed by or in consultation with a hematologist, an oncologist, or a physician who specializes in transplantation. Previously, criterion directed to a Medical Director and this criterion was removed. 2. **Cancer in Patients Receiving Myelosuppressive Chemotherapy:** This indication for use, and related criteria, were removed. **3. Myelodysplastic syndrome:** This indication for use was deleted. **4. Neuroblastoma:** Criteria were added that the patient is < 18 years of age and the phrase "Pediatric Patients with High Risk" was removed from the cited condition of approval..	08/21/2019
Annual Revision	No criteria changes.	08/19/2020

PRIOR AUTHORIZATION POLICY

POLICY: Colony Stimulating Factors – Pegfilgrastim Products Prior Authorization Policy

- Fulphila™ (pegfilgrastim-jmdb injection for subcutaneous use – Mylan)
- Neulasta® (pegfilgrastim injection for subcutaneous use [includes single-dose prefilled syringes for manual use and single-dose prefilled syringe co-packaged with the On-body Injector] – Amgen)
- Nyvepria™ (pegfilgrastim-apgf injection for subcutaneous use – Pfizer)
- Udenyca™ (pegfilgrastim-cbqv injection for subcutaneous use – Coherus)
- Ziextenzo™ (pegfilgrastim-bmez injection for subcutaneous use – Sandoz)

REVIEW DATE: 08/19/2020

OVERVIEW

Pegfilgrastim, a leukocyte growth factor, is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.[1-5] Fulphila, Nyvepria, Udenyca, and Ziextenzo are biosimilars to Neulasta. Neulasta is additionally indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) address the use of filgrastim products in guidelines for hematopoietic growth factors (version 2.2020 – January 27, 2020).[6] Guidelines recommend pegfilgrastim, along with other granulocyte colony stimulating factors (CSFs), for prophylactic use if the patient is receiving anti-cancer medications that are associated with a high (> 20%) incidence of severe neutropenia with fever.[5] Consider CSF therapy for patients with an intermediate (10% to 20%) probability of developing febrile neutropenia based on risk factors. The NCCN guidelines also endorse pegfilgrastim for the treatment of hematopoietic acute radiation syndrome and as supportive care post autologous hematopoietic cell transplant. NCCN recognize biosimilars as substitutes for Neulasta.

The American Society of Clinical Oncology clinical practice guidelines for the use of white blood cell growth factors (2015) recommends CSFs to reduce the risk of febrile neutropenia in patients receiving cancer chemotherapy.[7] CSFs may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected. The guidelines state CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of pegfilgrastim. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with pegfilgrastim as well as the monitoring required for adverse events and long-term efficacy, approval requires pegfilgrastim to be prescribed by or in consultation with a physician who specializes in the condition being treated.
Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of pegfilgrastim products is recommended in those who meet the following criteria:

FDA-Approved Indications

15. **Cancer in a Patient Receiving Myelosuppressive Chemotherapy**. Approve for 6 months if the patient meets the following criteria (A and B):
    - **A)** Patient meets ONE of the following conditions (i, ii, or iii):
        - **i.** Patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk is at least 20% based on the chemotherapy regimen); OR
        - **ii.** Patient is receiving myelosuppressive anti-cancer medications that are associated with a risk of febrile neutropenia but the risk is less than 20% based on the chemotherapy regimen and the patient has at least one risk factor for febrile neutropenia according to the prescriber; OR
          Note: Examples of risk factors include age ≥ 65 years; prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver and/or renal dysfunction; poor performance status; or human immunodeficiency virus (HIV) infection.
        - **iii.** The patient has had a neutropenic complication from prior chemotherapy and did not receive prophylaxis with a colony stimulating factor and a reduced dose or frequency of chemotherapy may compromise treatment outcome; AND
          Note: Examples of colony-stimulating factors include filgrastim products, pegfilgrastim products, and sargramostim products (e.g., Leukine®).
    - **B)** The medication is prescribed by or in consultation with an oncologist or hematologist.

12. **Radiation Syndrome (Hematopoietic Syndrome of Acute Radiation Syndrome).** Approve for 1 month if the agent is prescribed by or in consultation with a physician with expertise in treating acute radiation syndrome.

Other Uses with Supportive Evidence

13. **Peripheral Blood Progenitor Cell Transplantation in Patients with Cancer.** Approve one dose if prescribed by or in consultation with, an oncologist, a hematologist, or a physician who specializes in transplantation.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of pegfilgrastim products is not recommended in the following situations:

12. **Myelodysplastic Syndrome (MDS).** Only limited data report use of pegfilgrastim for patients with MDS.[8] Guidelines from the NCCN for MDS (version 2.2020 – February 28, 2020) do not mention use of pegfilgrastim in this patient population.[9]

13. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

25. Neulasta® injection for subcutaneous use [prescribing information]. Thousand Oaks, CA: Amgen, Inc.; April 2019.
26. Fulphila® injection for subcutaneous use [prescribing information]. Rockford, IL: Mylan; May 2019.
27. Udenyca™ injection for subcutaneous use [prescribing information]. Redwood City, CA: Coherus BioSciences; February 2019.
28. Ziextenzo™ injection for subcutaneous use [prescribing information]. Princeton, NJ: Sandoz; August 2019.
29. Nyvepria™ injection for subcutaneous use [prescribing information]. New York, NY: Pfizer, June 2020.
30. The NCCN Hematopoietic Growth Factors Clinical Practice Guidelines in Oncology (version 2.2020 – January 27, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 22, 2020.
31. Smith TJ, Bohlke K, Lyman GH, Carson KR, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2015;33(28):3199-3212.
32. Jakob A, Hirsch FW, Engelhardt M. Successful treatment of a patient with myelodysplastic syndrome (RAEB) with darbepoetin alfa in combination with pegfilgrastim. *Ann Hematol*. 2005;84(10):694-695.
33. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 2.2020 – February 28, 2020). ® 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 31, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Selected Revision	Selected revision to add Fulphila to the PA. Changed the PA policy to state "Pegfilgrastim Products" after" Colony Stimulating Factors".	06/13/2018
Annual Revision	For the criteria regarding patients with cancer receiving myelosuppressive therapy in the criteria that reference a colony stimulating factor, the terminology of filgrastim and pegfilgrastim products were added, along with the listing of the individual products, which included adding Nivestym and Fulphila.	08/01/2018
Selected Revision	For the indication regarding Patients with Cancer (Adults and Children) Receiving Myelosuppressive Chemotherapy, removed "(adults and children)".	08/08/2018
Selected Revision	Selected revision to add Udenyca to the PA.	12/05/2018
Annual Revision	Changes per the specific indication were as follows: **1. Cancer in Patients Receiving Myelosuppressive Chemotherapy:** CSFs are now provided as examples in a Note rather than as part of the criterion. Also, risk factors are now listed as Notes rather than as part of the criterion. The wording in reference to "according to the prescribing physician" was changed to "according to the prescriber".	08/21/2019
Selected Revision	Added Ziextenzo to the policy.	11/13/2019
Selected Revision	Added Nyvepria to the policy.	06/17/2020
Annual Revision	No criteria changes.	08/19/2020

PRIOR AUTHORIZATION POLICY

POLICY: Complement Inhibitors – Soliris Prior Authorization Policy

- Soliris® (eculizumab injection for intravenous use – Alexion)

REVIEW DATE: 05/27/2020; selected revision 09/16/2020

OVERVIEW

Soliris, a complement inhibitor, is indicated for the following uses:[1]

- **Atypical hemolytic uremic syndrome** (aHUS), to inhibit complement-mediated thrombotic microangiopathy.
- **Generalized myasthenia gravis** (gMG), in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.
- **Neuromyelitis optica spectrum disorder** (NMOSD), in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.

- **Paroxysmal nocturnal hemoglobinuria** (PNH), to reduce hemolysis.

Soliris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome. The safety and effectiveness of Soliris for the treatment of PNH, gMG, and NMOSD in pediatric patients have not been established. The safety and effectiveness of Soliris in pediatric patients for aHUS is supported by evidence from four adequate and well-controlled clinical studies assessing the safety and effectiveness of Soliris for the treatment of aHUS.

Disease Overview

Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles, which are responsible for breathing and moving parts of the body, including the arms and legs.[4] The hallmark of myasthenia gravis is muscle weakness that worsens after periods of activity and improves after periods of rest. Certain muscles such as those that control eye and eyelid movement, facial expression, chewing, talking, and swallowing are often involved in the disorder; however, the muscles that control breathing and neck and limb movements may also be affected. Acquired MG results from the binding of autoantibodies to components of the neuromuscular junction, most commonly the AChR.[5]

PNH is a rare disorder involving bone marrow failure that manifests with hemolytic anemia, thrombosis, and peripheral blood cytopenias.[6] Due to the absence of two glycosylphosphatidylinositol (GPI)-anchored proteins, CD55 and CD59, uncontrolled complement activation leads to hemolysis and other PNH manifestations. GPI anchor protein deficiency is often due to mutations in phosphatidylinositol glycan class A (PIGA), a gene involved in the first step of GPI anchor biosynthesis. PNH is a clinical diagnosis that should be confirmed with peripheral blood flow cytometry to detect the absence or severe deficiency of GPI-anchored proteins on at least two lineages. Prior to the availability of Soliris, there was no specific therapy for PNH with only supportive management in terms of the cytopenias and control of thrombotic risk. Supportive measures used include platelet transfusion, immune suppressive therapy for patients with bone marrow failure, use of erythropoietin for anemias, and aggressive anticoagulation. Soliris is the treatment of choice for patients with severe manifestations of PNH. Bone marrow transplantation is the only cure for PNH but should be reserved for patients with a suboptimal response to Soliris.

NMOSD is a rare, relapsing, autoimmune disorder of the brain and spinal cord with optic neuritis and/or myelitis as predominate characteristic symptoms.[2] NMOSD often causes significant, permanent damage to vision and/or spinal cord function causing blindness or impaired mobility.[3] Patients may experience pain, paralysis, loss of bowel and bladder control, loss of visual acuity, uncontrolled motor functions, and complications can cause death. Uplizna™ (inebilizumab-cdon injection for intravenous infusion) and Enspryng™ (satralizumab-mwge for subcutaneous injection) are two other FDA-approved medications for treatment of NMOSD in adults who are anti-AQP4 antibody-positive.[4,5] For acute attacks, typical treatment is high-dose intravenous corticosteroids.[6,7] Plasma exchange may be effective in patients who suffer acute severe attacks that do not response to intravenous corticosteroids. For long-term control of the disease a variety of immunosuppressive drugs are utilized as first-line therapy. While all are considered off-label use, corticosteroids, azathioprine, mycophenolate mofetil, and rituximab are treatments prescribed as preventative therapy.

Guidelines

An international consensus guidance for the management of MG was published in 2016 and do not address Soliris.[5] The guidelines recommend pyridostigmine for the initial treatment in most patients with MG. The ability to discontinue pyridostigmine can indicate that the patient has met treatment goals and may guide the tapering of other therapies. Corticosteroids or immunosuppressant therapy should be used in all patients with MG who have not met treatment goals after an adequate trial of pyridostigmine. Nonsteroidal immunosuppressant agents include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. It is usually necessary to maintain some immunosuppression for many years, sometimes for life. Plasma exchange and intravenous immunoglobulin can be used as short-term treatments in certain patients. The guidelines note that few physicians treat enough patients with MG to be comfortable with all available treatments.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Soliris. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of

the specialized skills required for evaluation and diagnosis of patients treated with Soliris as well as the monitoring required for adverse events and long-term efficacy, approval requires Soliris to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Soliris is recommended in those who meet the following criteria:

FDA-Approved Indications

25. Atypical Hemolytic Uremic Syndrome. Approve for 1 year if the patient meets the following criteria (A and B):
- **20.** Patient does not have Shiga toxin *E. coli* related hemolytic uremic syndrome; AND
- **21.** The medication is being prescribed by or in consultation with a nephrologist.

26. Generalized Myasthenia Gravis. Approve if the patient meets ONE of the following criteria (A or B):

B) Initial therapy: Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv, v, and vi):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient has confirmed anti-acetylcholine receptor antibody positive generalized Myasthenia Gravis; AND
- **iii.** Patient is currently receiving or has tried and has contraindications, intolerance, or failed pyridostigmine; AND
- **iv.** Patient is currently receiving or has tried and has contraindications, intolerance, or failed two different immunosuppressant therapies over ≥ 1 year; AND
  Note: Examples of immunosuppressant therapies tried include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus, cyclophosphamide.
- **v.** Patient has evidence of unresolved symptoms of generalized Myasthenia Gravis, such as difficulty swallowing, difficulty breathing, or a functional disability resulting in the discontinuation of physical activity (e.g., double vision, talking, impairment of mobility); AND
- **vi.** The medication is being prescribed by or in consultation with a neurologist.

C) Patient currently receiving Soliris. Approve for 1 year if the patient is continuing to derive benefit from Soliris, according to the prescriber.
Note: Examples of derived benefit include reductions in exacerbations of myasthenia gravis; improvements in speech, swallowing, mobility, and respiratory function.

27. Neuromyelitis Optica Spectrum Disorder. Approve if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 1 year if the patient meets the following criteria (i, ii, iii, iv, and v):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Neuromyelitis optica spectrum disorder diagnosis was confirmed by blood serum test for anti-aquaporin-4 antibody positive; AND
- **iii.** Patient is currently receiving or has previously tried two of the following systemic therapies (a, b, c, or d):
  - **a.** Azathioprine; OR
  - **b.** Corticosteroid; OR
  - **c.** Mycophenolate mofetil; OR
  - **d.** Rituximab; AND
    Note: An exception to the requirement for a trial of a systemic therapy can be made if the patient has already tried Enspryng™ (satralizumab-mwge for subcutaneous injection) or Uplizna™ (inebilizumab-cdon injection) for neuromyelitis optica spectrum disorder. Patients who have already tried Enspryng or Uplizna for neuromyelitis optica spectrum disorder are not required to try another systemic agent.
- **iv.** Patient has a history of at least 1 relapse in the last 12 months or two relapses in the last 2 years; AND
- **v.** The medication is being prescribed by or in consultation with a neurologist.

B) Patients Currently Receiving Soliris. Approve for 1 year if the patient meets the following (i, ii, iii, and iv):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Neuromyelitis optica spectrum disorder diagnosis was confirmed by blood serum test for anti-aquaporin-4 antibody positive; AND
- **iii.** According to the prescriber, patient has had clinical benefit from the use of Soliris; AND
  Note: Examples of clinical benefit include reduction in relapse rate, reduction in symptoms (e.g., pain, fatigue, motor function), and a slowing progression in symptoms.
- **iv.** The medication is being prescribed by or in consultation with a neurologist.

28. Paroxysmal Nocturnal Hemoglobinuria. Approve if the patient meets ONE of the following (A or B):

A) Initial therapy: Approve for 6 months if the patient meets the following criteria (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Paroxysmal nocturnal hemoglobinuria diagnosis was confirmed by peripheral blood flow cytometry results showing the absence or deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins on at least two cell lineages; AND
- **iii.** The medication is being prescribed by or in consultation with a hematologist; OR

B) Patient currently receiving Soliris: Approve for 1 year if the patient is continuing to derive benefit from Soliris, according to the prescriber.
Note: Examples of derived benefit include stabilization of hemoglobin levels, decreased transfusion requirements or transfusion independence, reductions in hemolysis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Soliris is not recommended in the following situations:

14. Concomitant use with a rituximab product, Enspryng™ (satralizumab-mwge), or Uplizna™ (inebilizumab-cdon injection). There is no evidence to support additive efficacy of combining Soliris with rituximab, Enspryng or Uplizna.

15. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	05/16/2018
Annual Revision	No change to criteria.	05/29/2019
Selected Revision	**Neuromyelitis Optica Spectrum Disorder** approval **Criteria** were added to the FDA-approved indications section of the policy.	08/07/2019
Annual Revision	No changes to criteria.	05/27/2020
Selected Revision	**Generalized Myasthenia Gravis (gMG).** Examples of immunosuppressant therapies were changed to a Note. For patients currently receiving Soliris, examples of the patient continuing to derive benefit was changed to a Note and prescribing physician was changed to prescriber. **Paroxysmal Nocturnal Hemoglobinuria.** For patients currently receiving Soliris, examples of the patient continuing to derive benefit was changed to a Note and prescribing physician was changed to prescriber. **Neuromyelitis Optica Spectrum Disorder.** Criteria was separated into Initial Therapy and Patients Currently Receiving Soliris. For both sections, criteria for approval duration, age restriction, diagnosis confirmation, and specialist requirement remained the same as before. For Initial Therapy, a Note was created to allow an exception to previously tried systemic therapies for patients who have tried Enspryng or Uplizna. Criteria for a history of previous relapses were added. For Patients Currently Receiving Soliris, criteria were added to show the patient is receiving a clinical benefit from Soliris. **Concomitant use with a rituximab product, Soliris® (eculizumab injection), or Enspryng™ (satralizumab-mwge injection)** was added as a condition not recommended for approval.	09/09/2020

PRIOR AUTHORIZATION POLICY

POLICY: Complement Inhibitors – Ultomiris Prior Authorization Policy

- Ultomiris™ (ravulizumab-cwvz injection for intravenous use – Alexion)

REVIEW DATE: 11/04/2020

OVERVIEW

Ultomiris, a complement inhibitor, is indicated for the following uses:[1]

- **Atypical hemolytic uremic syndrome** (aHUS), in adults and pediatric patients one month of age and older.
- **Paroxysmal nocturnal hemoglobinuria** (PNH), in adults.

The safety and effectiveness of Ultomiris for the treatment of PNH in pediatric patients have not been established.[1] PNH is a clinical diagnosis that should be confirmed with peripheral blood flow cytometry to detect the absence or severe deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins on at least two lineages.[2] The recommended dosing regimen for adults with PNH consists of a weight-based loading dose (dosage range: 2,400 mg to 3,000 mg) followed by maintenance dosing (dosage range: 3,000 mg to 3,600 mg), administered by intravenous (IV) infusion.[1] Starting 2 weeks after the loading dose administration, begin maintenance doses at a once every 8-week interval. The recommended dosing regimen for patients with aHUS consists of a weight-based loading dose (dosage range: 600 mg to 3,000 mg) followed by maintenance dosing (dosage range: 300 mg to 3,600 mg), administered by IV infusion. Starting 2 weeks after the loading dose administration, begin maintenance doses at a once every 4-week interval for patients ≥ 5 kg to < 20 kg or at a once every 8-week interval for patients ≥ 20 kg. For both PNH and aHUS the dosing schedule is allowed to occasionally vary within 7 days of the scheduled infusion day (with the exception of the first maintenance dose) but the subsequent dose should be administered according to the original schedule.

Disease Overview

Hemolytic uremic syndrome (HUS) is defined as the triad of non-immune hemolytic anemia, thrombocytopenia, and acute renal failure, in which the underlying lesions are mediated by systemic thrombotic microangiopathy (TMA).[4]

The TMA process that characterizes HUS can be caused by a variety of things. Atypical HUS (aHUS) is a sub-type of HUS in which TMA are the consequence of endothelial damage in the microvasculature of the kidneys and other organs due to a dysregulation of the activity of the complement system. Various aHUS-related mutations have been identified in genes of the complement system, which can explain approximately 60% of the aHUS cases, and a number of mutations and polymorphisms have been functionally characterized. aHUS should be distinguished from a more common condition referred to as typical HUS.[5] The two disorders have different causes and different signs and symptoms. Unlike aHUS, the typical form is caused by infection with certain strains of *Escherichia coli* (*E. coli*) bacteria that produce toxic substances called Shiga-like toxins. The typical form is characterized by severe diarrhea and most often affects children < 10 years of age, and it is less likely than aHUS to involve recurrent attacks of kidney damage that lead to end stage renal disease (ESRD). The incidence of aHUS is estimated to be 1:500,000 people/year in the US; aHUS is approximately 10 times less common than typical HUS.

PNH is a rare disorder involving bone marrow failure that manifests with hemolytic anemia, thrombosis, and peripheral blood cytopenias.[2] Due to the absence of two GPI-anchored proteins, CD55 and CD59, uncontrolled complement activation leads to hemolysis and other PNH manifestations. GPI anchor protein deficiency is often due to mutations in phosphatidylinositol glycan class A (PIGA), a gene involved in the first step of GPI anchor biosynthesis. Prior to the availability of Soliris® (eculizumab injection for IV) [a complement inhibitor][3], there was no specific therapy for PNH with only supportive management in terms of the cytopenias and control of thrombotic risk. Supportive measures used include platelet transfusion, immune suppressive therapy for patients with bone marrow failure, use of erythropoietin for anemias, and aggressive anticoagulation. Soliris is the treatment of choice for patients with severe manifestations of PNH. Bone marrow transplantation is the only cure for PNH but should be reserved for patients with a suboptimal response to medication.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ultomiris. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ultomiris as well as the monitoring required for adverse events and long-term efficacy, approval requires Ultomiris to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ultomiris is recommended in those who meet the following criteria:

FDA-Approved Indications

29. Paroxysmal Nocturnal Hemoglobinuria. Approve for the duration noted if the patient meets ONE of the following (A or B):

B) Initial therapy: Approve Ultomiris for 6 months if the patient meets the following criteria (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Paroxysmal nocturnal hemoglobinuria diagnosis was confirmed by peripheral blood flow cytometry results showing the absence or deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins on at least two cell lineages; AND
- **iii.** Ultomiris is being prescribed by or in consultation with a hematologist; OR

C) Patient currently receiving Ultomiris: Approve Ultomiris for 1 year if the patient is continuing to derive benefit from Ultomiris, according to the prescriber.
Note: Examples of benefit from Ultomiris include stabilization of hemoglobin levels, decreased transfusion requirements or transfusion independence, reductions in hemolysis.

30. Atypical Hemolytic Uremic Syndrome. Approve for 1 year if the patient meets the following criteria (A and B):
- **22.** Patient does not have Shiga toxin *E. coli* related hemolytic uremic syndrome; AND
- **23.** Ultomiris is being prescribed by or in consultation with a nephrologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ultomiris is not recommended in the following situations:

16. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/24/2018
Early Annual Revision	The condition of Atypical Hemolytic Uremic Syndrome and criteria were added to the policy within the FDA-approved indications.	11/06/2019
Annual Revision	**Paroxysmal Nocturnal Hemoglobinuria.** For patients currently receiving Ultomiris, the wording of "prescribing physician" was changed to "prescriber". Also, examples of benefit from Ultomiris were changed to a Note.	11/04/2020

PRIOR AUTHORIZATION POLICY

POLICY: Compounded Select Topical Medications (topical ketamine, topical gabapentin, topical diclofenac, topical ketoprofen, topical flurbiprofen, topical nabumetone, topical meloxicam, topical hyaluronic acid, topical mometasone furoate, topical fluticasone propionate)

DATE REVIEWED: 05/13/2020

OVERVIEW

Compounded products are used for a variety of indications from treating pain to hormone therapy. The compounded formulations can contain just one active drug in a base vehicle or they may contain a combination of active drugs. Compounded medications are not Food and Drug Administration (FDA) approved, thus the FDA has limited regulatory authority over compounding pharmacies since they are licensed by their respective state board of pharmacy. Compounded medications also do not undergo the rigorous drug review process to demonstrate safe and effective use in patients that all commercially available prescription drugs must establish prior to widespread availability. Also, compounded medications generally do not have standardized dosages and duration for use; likewise, there are no standardized protocols to prepare each compound. For these reasons, compounded preparations are at a greater propensity to have batch-to-batch variability and the product sterility/purity cannot be guaranteed relative to the commercially available products.

EFFICACY

There are very limited published controlled studies with established safety and efficacy data supporting use of compounded medications for any condition. The available efficacy data for the targeted topical compounds in this policy are described below.

Topical Ketamine

There are four randomized, placebo-controlled studies published assessing the use of compounded topical ketamine for neuropathic pain. *Study 1* enrolled patients (n = 208) with chemotherapy-induced peripheral neuropathy (CIPN) and randomized them to either a placebo gel or a compounded mixture containing baclofen 10 mg, amitriptyline 40 mg, and ketamine 20 mg in a pluronic lecithin organogel (BAK-PLO) vehicle base.[1] Patients applied the gel twice daily (BID) for 4 weeks. There was a trend towards improvement in the sensory neuropathy scale (primary endpoint) compared with placebo, though it was not statistically significant (P = 0.053). Statistically significant improvement was noted with the motor subscale (P = 0.021). *Study 2* enrolled patients (n = 92) with mixed neuropathic pain (i.e., diabetic neuropathy [n = 20/92], postherpetic neuralgia [n = 14/92], post-surgical/post-traumatic neuropathic pain [n = 58/92] with allodynia, hyperalgesia, or pinprick hyperthesia) and evaluated the application of one of four topical creams: topical amitriptyline 2%, topical ketamine 1%, a combination of topical amitriptyline 2% and topical ketamine 1%, or placebo (vehicle base).[2] Patients applied 4 mL cream to the site of maximum pain three times daily (TID) for 3 weeks. Pain levels at the end of the study compared with baseline were not statistically significant between treatment groups. *Study 3* evaluated the efficacy of topical ketamine 5% cream applied TID for 4 weeks in patients (n = 17) with diabetic neuropathy.[3] Seven different pain characteristics (i.e., intensity, sharpness, cold, hot, dull, sensitive, and itchy) were measured using a pain scale both before and after treatment. Diabetic pain measures were reduced in both treatment groups and the placebo effect was equally as strong as ketamine 5% cream. *Study 4* was a cross-over trial that assessed the efficacy of (S)-ketamine 1% ointment or placebo applied four times daily (QID) for 15 days in patients (n = 12) with postherpetic neuralgia.[4] There was a wash-out period of 7 days in-between crossover. A numerical verbal scale was used to assess pain scores and efficacy of therapy during three different clinic visits. There was no statistical significance in pain scores during treatments with (S)-ketamine 1% ointment or placebo.

One small randomized, double-blind, placebo-controlled study assessed the use of compounded topical ketamine in patients (n = 20) with complex regional pain syndrome (CRPS).[5] CRPS has been described as a challenging pain syndrome usually starting after a trauma or surgery.[6] CRPS can be classified into two types: patients with CRPS type 1 do not have demonstrable nerve lesions and type 2 is based on objective nerve damage, most commonly caused by severe trauma. CRPS type 1 has also been recognized as a chronic neuropathic pain syndrome that typically develops in an extremity after tissue trauma. The above mentioned study[5] concluded that topical ketamine did not lead to pain reduction in patients with CRPS, but it did reduce allodynia to brushing.

Topical Gabapentin

There are no published data available with the use of compounded topical gabapentin for neuropathic pain.

The only published trial available is a retrospective study assessing the use of topical gabapentin 2% to 6% cream in women (n = 51) with vulvodynia (chronic, unexplained vulvar pain or discomfort, characterized by burning, stinging, irritation or rawness).[7] After a minimum of 8 weeks of therapy with application of gabapentin cream TID, about 80% of the patients demonstrated at least a 50% improvement in their pain scores. The British Society for the Study of Vulval Diseases guidelines (2010) for the management of vulvodynia do not list topical gabapentin as a therapeutic choice (oral gabapentin is considered an option).[8]

Topical Hyaluronic Acid Sodium Salt

Hyaluronic acid is a naturally occurring polysaccharide that is widely distributed in various body tissues.[9] Sodium hyaluronate and other derivatives are used for a variety of conditions, such as osteoarthritis (OA), and as surgical aid in ophthalmic procedures. It is available commercially as FDA-approved products in various dosage forms: as intra-articular injections (e.g., Synvisc®) for the treatment of knee OA; as ophthalmic solution for irrigation (e.g., Vitrax®); and as topical spray, cream, and gel products for use in wound care (e.g., Hylase® wound gel, Bionect® topical gel, cream, spray). There are also multiple

hyaluronic acid products available as intradermal injectable gel for use as wrinkle fillers in cosmetic procedures (e.g., Juvederm® XC). Most of the hyaluronic acid products were approved as devices by the FDA.

There are limited published data available with the use of compounded topical hyaluronic acid as vaginal suppositories for the treatment of vaginal atrophy in postmenopausal women.[10-14] If over-the-counter (OTC) vaginal moisturizers were ineffective as initial treatment, prescription vaginal estrogen therapy is the recommended first-line agent for the treatment of symptomatic vaginal atrophy.[15]

Topical Corticosteroids – Fluticasone Propionate, Mometasone Furoate
Fluticasone propionate and mometasone furoate are corticosteroids which are used intranasally for the treatment of allergic and non-allergic rhinitis, by oral inhalation for the treatment of asthma and/or chronic obstructive pulmonary disease (COPD), and as topical preparations for the treatment of inflammatory and pruritic types of dermatoses and psoriasis.[9] These two corticosteroids are available as FDA-approved, commercial products in the following strengths and dosage form: fluticasone propionate 0.05% cream, lotion, and as 0.005% ointment; mometasone furoate 0.1% cream, lotion, and ointment.
There are no published clinical trial data available for the use of compounded topical formulations of fluticasone propionate or mometasone furoate either alone or in combination with other products for the treatment of skin conditions. One small open-label study (n = 23) evaluated the use of intranasal irrigation of fluticasone propionate in post-endoscopic sinus surgery patients with chronic rhinosinusitis.[16] The main intent of this study was to assess the effects of fluticasone on adrenal function (whether or not it was suppressed) and its effect on intraocular pressure (IOP). The irrigation solution was prepared by emptying a 3-mg capsule of fluticasone propionate (provided by a compounding pharmacy) into 240 mL isotonic saline solution (available OTC as Sinus Rinse™ saline rinse kit) and used twice daily for 6 weeks. There were no significant changes with fluticasone irrigation use in measured salivary cortisol levels or IOP after 6 weeks. No other efficacy data are noted in this study.

Topical Non-Steroidal Anti-inflammatory Drugs (NSAIDs)
The other compounded topical drugs targeted in this policy – topical diclofenac, ketoprofen, flurbiprofen, meloxicam, and nabumetone – all belong to the NSAID drug class. These agents are generally used for the treatment of pain (e.g., OA, musculoskeletal pain). There are several topical NSAID formulations that are FDA-approved and commercially available. Topical diclofenac is commercially available as Solaraze® 3% gel, Voltaren® 1% gel, Pennsaid® 1.5% topical solution, Voltaren® 0.1% ophthalmic solution, and as Flector® 1.3% topical patch.[17-21] Voltaren gel is indicated for the treatment of OA in knees and hands, and Pennsaid is indicated for the treatment of OA of the knees.[18-19] Topical flurbiprofen is commercially available as Ocufen® 0.03% ophthalmic solution and it is indicated for the treatment of intraoperative miosis.[22] The American College of Rheumatology (ACR) guidelines (2012) for hand, hip, and knee OA recommend topical NSAIDs for the treatment of hand and knee OA.[23] It is important to note that these guidelines are only referring to FDA-approved topical NSAIDs, as literature searches were limited to only commercially available NSAID formulations in the US and Canada.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of the following compounded topical medications: ketamine, gabapentin, diclofenac, ketoprofen, flurbiprofen, meloxicam, nabumetone, hyaluronic acid derivatives, mometasone furoate, and fluticasone propionate. Due to the lack of robust clinical efficacy and safety data, in addition to the lack of standardized dosages and formulations, **approval is not recommended for any condition** for these non-FDA-approved topical compounded formulations of ketamine, gabapentin, diclofenac, ketoprofen, flurbiprofen, meloxicam, nabumetone, hyaluronic acid derivatives, mometasone furoate, and fluticasone propionate (either alone or in combination with other medications).

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Compounded topical formulations of ketamine, gabapentin, diclofenac, ketoprofen, flurbiprofen, meloxicam, nabumetone, hyaluronic acid derivatives, mometasone furoate, and fluticasone propionate (either alone or in combination with other medications) have not been shown to be effective or there are limited or preliminary data that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

Topical Ketamine

83. Neuropathic Pain. There are published data available from four randomized, placebo-controlled studies assessing the efficacy of compounded topical ketamine, either alone or in combination with other agents (e.g., amitriptyline, baclofen) for the treatment of various types of neuropathic pain (e.g., peripheral neuropathy, diabetic neuropathy).[1-4] In summary, three of the four studies did not show any statistically significant efficacy differences compared with placebo. One study showed a trend towards improvement compared with placebo in patients with CIPN.[1] All of the other published data with topical ketamine use for neuropathic pain are based on case reports, open-label studies, or pilot studies.

84. Complex regional pain syndrome (CRPS). There are very limited published efficacy data available with topical ketamine for the treatment of CRPS. One small double-blind, placebo-controlled study assessed the efficacy of ketamine 10% cream in patients (n = 20) with CRPS type 1 (n = 18/20) and type 2 (n = 2/20) on two separate occassions.[5] The primary aim was to determine whether topical ketamine inhibited sensory disturbances in the symptomatic limb of patients. Topical ketamine did not lead to pain reduction, but allodynia to brushing the skin was reduced. Most of the other published evidence for topical ketamine use for CRPS is based on case reports.

Topical Gabapentin

1. Neuropathic Pain. There are no published efficacy or safety data available with compounded topical formulations of gabapentin either alone or in combination with other drugs for use in neuropathic pain.

2. Complex regional pain syndrome (CRPS). There are no published efficacy or safety data available with topical gabapentin use for the treatment of CRPS.

3. Vulvodynia. There is one retrospective study that assessed the efficacy of topical gabapentin 2% to 6% in women (n = 51) with vulvodynia.[7] Though topical gabapentin was effective in reducing pain in about 80% of women, these data are limited by small sample size and study design. Large randomized trials are needed to establish the efficacy of topical gabapentin for vulvodynia.

Topical NSAIDs (diclofenac, ketoprofen, flurbiprofen, nabumetone, and meloxicam)

1. Arthritis (e.g., osteoarthritis [OA], rheumatoid arthritis [RA]). There are no published data available with the use of compounded, non-FDA approved topical formulations of NSAIDs such as topical diclofenac, topical ketoprofen, topical meloxicam, topical nabumetone, or topical flurbiprofen, either alone or in combination with other agents for the treatment of arthritis, such as OA. FDA-approved, commercially available topical NSAIDs such as Voltaren 1% gel, and Pennsaid 1.5% topical solution are indicated for the treatment of OA and have substantial efficacy and safety data supporting their use.[10-11] With the availability of effective and safe FDA-approved topical NSAIDs, the use of other compounded topical NSAIDs with no established efficacy and safety data is not recommended.

Topical Fluticasone Propionate and Mometasone Furoate

1. **Use in various types of skin conditions (e.g., dermatitis, wound care).** There are very limited to no published efficacy or safety data available with non-FDA approved, compounded formulations of fluticasone and mometasone for the treatment of skin conditions.

2. **Cosmetic Use (e.g., scar therapy, for minimizing stretch marks).** Cosmetic use is excluded from coverage in a typical pharmacy benefit.

3. **Use as Intranasal Irrigation Solution for Chronic Rhinosinusitis.** One small study (n = 23) assessed the use of fluticasone propionate 3 mg in 240 mL saline, as irrigation solution twice daily in patients with chronic rhinosinusitis who had undergone sinus surgery.[16] The study mainly assessed for the effects of fluticasone on salivary cortisol levels and ocular changes. There are no other published efficacy or safety data with the use of corticosteroids in irrigation solutions.

Topical Hyaluronic Acid Derivatives

1. **Vaginal Atrophy.** Limited data are available with the use of hyaluronic acid derivatives in combination with other agents (e.g., vitamin E) for the treatment of vaginal atrophy;[10-14] however, vaginal estrogen therapies are the recommended first-line agents for the treatment of symptomatic vaginal atrophy.[15]

2. **Osteoarthritis (OA).** There are no published efficacy data available to support the use of non-FDA -approved, compounded formulations of hyaluronic acid and its derivatives for use in any OA or other pain-related conditions. Hyaluronic acid intra-articular injections (e.g., Synvisc) are available as FDA-approved products for the treatment of OA of the knee.[9]

3. **Use in Any Other Medical Condition, Including, But Not Limited to Ophthalmic Procedures and Wound Care.** There are no published efficacy data available to support the use of non-FDA- approved, compounded formulations of hyaluronic acid and its derivatives for use in any medical condition.

4. **Cosmetic Use (e.g., treatment of frown lines).** Cosmetic use is excluded from coverage in a typical pharmacy benefit.

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HISTORY

Type of Revision	Summary of Changes*	Date Reviewed
Integrated policy	New policy	05/29/2013
Early Annual revision	Added compounded topical meloxicam, nabumetone, hyaluronic acid, fluticasone propionate, and mometasone furoate to policy.	03/05/2014
Annual revision	No criteria changes	03/18/2015
Annual revision	No criteria changes	03/30/2016
Annual revision	No criteria changes	04/05/2017
Annual revision	No criteria changes	04/11/2018
Annual revision	No criteria changes	04/17/2019
Annual revision	No criteria changes	05/13/2020

PRIOR AUTHORIZATION POLICY

POLICY: Contraceptives – Phexxi Prior Authorization Policy

- Phexxi™ (lactic acid, citric acid, and potassium bitartrate vaginal gel – EvoFem Biosciences, Inc.)

REVIEW DATE: 11/04/2020

OVERVIEW

Phexxi is indicated for the **prevention of pregnancy** in females of reproductive potential for use as an on-demand method of contraception.[1] Limitation of Use: Phexxi is not effective for the prevention of pregnancy when administered after intercourse.

Phexxi contains lactic acid, citric acid, and potassium bitartrate; *in vitro* studies show that a pH lowering effect and sperm motility reduction contribute to the activity of the product in the vagina.[1] Phexxi has been previously known under multiple names, such as Amphora, Acidform, and was historically available as an over-the-counter (OTC) personal lubricant.[2] The recommended dose of Phexxi is one pre-filled applicator

(5 grams) vaginally administered immediately before or up to one hour before each act of vaginal intercourse.[1] If more than one act of vaginal intercourse occurs within one hour, an additional dose must be used.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Phexxi. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Phexxi is recommended in those who meet the following criteria:

FDA-Approved Indications

14. Prevention of Pregnancy. Approve for 6 months if the patient has tried THREE other barrier methods of contraception (i.e., diaphragms, condoms, spermicides, or sponges).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Phexxi is not recommended in the following situations:

17. As a Personal Lubricant. The ingredients in Phexxi were previously available and marketed as an OTC personal lubricant.[2] Phexxi is currently only indicated for prevention of pregnancy.[1]

18. Acute Episodes of Bacterial Vaginosis. Low vaginal pH may provide a measure of protection against specific organisms.[2] In a pilot clinical study comparing Acidform gel with metronidazole gel for the treatment of symptomatic bacterial vaginosis, Acidform gel was significantly less effective.[3]

19. For Protection Against Human Immunodeficiency Virus (HIV) or any other Sexually Transmitted Infections. Per Phexxi labeling, it does not protect against HIV infection and other sexually transmitted infections.[1]

20. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	11/04/2020

PRIOR AUTHORIZATION POLICY

POLICY: Coronavirus Disease – Veklury Prior Authorization Policy

- Veklury® (remdesivir injection – Gilead Sciences, Inc.)

REVIEW DATE: 11/04/2020

OVERVIEW

Veklury, a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleotide analog RNA polymerase inhibitor, is indicated for the treatment of **coronavirus disease 19 (COVID-19)** in patients ≥ 12 years of age and weighing ≥ 40 kg, who require hospitalization.[1]

Guidelines

The Infectious Disease Society of America (IDSA) and the National Institutes of Health (NIH) have developed treatment guidelines for the management of COVID-19 and each address the use of Veklury.[2,3] Both the IDSA and NIH guidelines recommend Veklury for hospitalized patients with COVID-19 who require supplemental oxygen. For patients receiving supplemental oxygen, Veklury is recommended for 5 days of treatment, and patients receiving invasive mechanical ventilation or extracorporeal membrane oxygenation should be treated with Veklury for 10 days.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Veklury. All approvals are provided for the duration noted below. All reviews will be forwarded to the Medical Director for evaluation.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Veklury is recommended in those who meet the following criteria:

FDA-Approved Indications

15. Coronavirus Disease 2019 (COVID-19), Treatment. Approve for 10 days if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 12 years of age; AND
- **B)** Patient has tested positive for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); AND
- **C)** Patient is being treated in a hospital.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Veklury is not recommended in the following situations:

21. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	11/04/2020

PRIOR AUTHORIZATION POLICY

POLICY: Crysvita Prior Authorization Policy

- Crysvita® (burosumab-twza injection, subcutaneous use – Ultragenyx)

REVIEW DATE: 05/27/2020; selected revision 07/22/2020

OVERVIEW

Crysvita, a fibroblast growth factor 23 (FGF23) blocking antibody, is indicated for[1]:

- **X-linked hypophosphatemia** in patients ≥ 6 months of age.
- **Tumor-induced osteomalacia**, for treatment of FGF-related hypophosphatemia associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in patients ≥ 2 years of age.

Disease Overview

X-Linked Hypophosphatemia

X-linked hypophosphatemia is a condition that is believed to result from an inactivating genetic mutation in phosphate regulating endopeptidase on the X chromosome (PHEX).[2-4] This mutation leads to increased levels of FGF23, which increases phosphate excretion and abnormal vitamin D metabolism, ultimately leading to hypophosphatemic rickets.[2-5] Pediatric patients (usually < 2 years of age) usually present with bowing deformities of the lower extremities and short stature. In adults, symptoms include calcification of tendons, ligaments, and joint capsules, joint pain, impaired mobility, spontaneous dental abscesses, stress fractures, and sensorineural hearing loss. The X-linked hypophosphatemia diagnosis can be established in patients with a low serum phosphate concentration, a reduced tubular resorption of phosphate corrected for glomerular filtration rate (TmP/GFR), an inappropriate calcitriol level for the severity of hypophosphatemia, and/or by identification on molecular genetic testing of a hemizygous PHEX pathogenic variant in a male patient or a heterozygous PHEX pathogenic variant in a female patient. Genetic testing is estimated to identify mutations in the PHEX gene in approximately 70% of patients with hypophosphatemic rickets and 85% to 90% of patients who have familial hypophosphatemic rickets.[6]

Tumor-Induced Osteomalacia

Tumor-induced osteomalacia is an extremely rare condition caused by tumors that produce the phosphaturic hormone FGF23.[7] Elevated FGF23 causes renal phosphate wasting, which ultimately leads to hypophosphatemia, rickets, and osteomalacia. Tumor-induced osteomalacia is generally caused by small, slow-growing, benign phosphaturic mesenchymal tumors; complete resection of the tumor results in cure. However, in some cases, locating the tumor is not possible or the tumor may be inoperable. Patients usually present in adulthood with symptoms of fatigue, muscle weakness, and pain.[8] They may also experience decreased bone mineral density and frequent fractures. Current treatment of patients with inoperable or unidentifiable tumors has been phosphate supplementation and active vitamin D.

Clinical Efficacy

X-Linked Hypophosphatemia

The efficacy of Crysvita for the treatment of X-linked hypophosphatemia was evaluated in several clinical in pediatric and adult patients with X-linked hypophosphatemia.[1] Eligible patients had baseline serum phosphorus levels less than the lower limit of normal for age.[1,9-11] Across the studies, Crysvita was found

to increase mean serum phosphorus levels significantly from baseline. Radiographic improvements and healing of fractures/pseudofractures were also observed. In a single-arm extension of the adult study, normalization of serum phosphorous was maintained during an additional 24 weeks of Crysvita therapy.[12] Improvements in healing of fractures/pseudofractures were also observed. One additional study compared Crysvita with conventional therapy in patients 1 to 12 years of age with X-linked hypophosphatemia.[13] Following 64 weeks of therapy, patients receiving Crysvita had demonstrated a significantly greater improvement in the Radiographic Global Impression of Change global score compared with the conventional therapy group.

Tumor-Induced Osteomalacia

Two studies evaluated the efficacy of Crysvita in patients with tumor-induced osteomalacia.[1,14] Eligible patients were adults with a confirmed diagnosis of FGF-23-related hypophosphatemia produced by an underlying tumor that was not amenable to surgical excision or could not be located. In addition to low baseline serum phosphorus, patients were also required to have a low tubular reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR) and a high FGF23 level. The vast majority of patients had previously received phosphate and active vitamin D therapy. Crysvita was found to increase the mean serum phosphorus level from baseline through Week 24 (Month 6) when levels stabilized. These increases were sustained near or above the lower limit of normal through Week 144.

Guidelines

X-Linked Hypophosphatemia

In 2019, an expert panel published Clinical Practice Recommendations for the Diagnosis and Management of X-linked hypophosphatemia.[13] This document recommends treatment with oral phosphate and active vitamin D (e.g., calcitriol) for symptomatic adults with X-linked hypophosphatemia. Crysvita therapy should be considered for the treatment of adults with X-linked hypophosphatemia with the following features: persistent bone/joint pain due to X-linked hypophosphatemia and/or osteomalacia that limits daily activities; pseudofractures or osteomalacia-related fractures; and insufficient response or refractory to oral phosphate and active vitamin D. If patients experience complications related to oral phosphate and active vitamin D, Crysvita is recommended as well.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Crysvita. Because of the specialized skills required for evaluation and diagnosis of patients treated with Crysvita as well as the monitoring required for adverse events and long-term efficacy, approval requires Crysvita to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Crysvita is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **X-Linked Hypophosphatemia.** Approve Crysvita for the duration noted if the patient meets ONE of the following criteria (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets ALL of the following criteria (i, ii, iii, and iv):

i. Patient has had a baseline (prior to any X-linked hypophosphatemia treatment) serum phosphorus level that was below the normal range for age; AND
Note: Examples of X-linked hypophosphatemia treatment include Crysvita, oral phosphate/vitamin D therapy.

ii. Patient meets ONE of the following (a or b):
- **a)** Patient has had a baseline (prior to any X-linked hypophosphatemia treatment) tubular reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR) that was below the normal range for age and gender; OR
  Note: Examples of X-linked hypophosphatemia treatment include Crysvita, oral phosphate/vitamin D therapy.
- **b)** Patient has had a genetic test confirming the diagnosis of X-linked hypophosphatemia via identification of a PHEX mutation; AND

iii. If the patient is ≥ 18 years of age, the patient meets BOTH of the following (a and b):
- **a)** Per the prescriber, the patient is currently exhibiting one or more signs or symptoms of X-linked hypophosphatemia; AND
  Note: Examples of signs and symptoms of X-linked hypophosphatemia in patients ≥ 18 years of age include fractures/pseudofractures, bone and joint pain, muscle weakness, and impaired mobility.
- **b)** Patient meets ONE of the following (1 or 2):
  - **a)** Patient has tried oral phosphate and calcitriol therapy; OR
  - **b)** Per the prescriber the patient has a contraindication to oral phosphate therapy, calcitriol therapy, or both; AND

iv. The medication is prescribed by or in consultation with an endocrinologist or nephrologist.

B) Patient is Currently Receiving Crysvita. Approve for 1 year if the patient is continuing to derive benefit from Crysvita as determined by the prescriber.
Note: Examples of a response to Crysvita therapy are increased phosphorus levels, radiographic improvement in deformities, healing of fractures/pseudofractures, reduction in the incidence of new fractures/pseudofractures.

2. Tumor-Induced Osteomalacia. Approve Crysvita for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following criteria (i, ii, iii, iv, v, vi and vii):

i. Patient is ≥ 2 years of age; AND

ii. Patient has a mesenchymal tumor that cannot be curatively resected or identified/localized; AND

iii. Per the prescriber, the patient is currently exhibiting one or more signs or symptoms of tumor-induced osteomalacia; AND
Note: Examples of signs and symptoms of tumor-induced osteomalacia include bone pain, impaired mobility, muscle weakness, and fatigue.

iv. Patient has had a baseline (prior to any tumor-induced osteomalacia treatment) serum phosphorus level that was below the normal range for age; AND
Note: Examples of tumor-induced osteomalacia treatment include Crysvita, oral phosphate/vitamin D therapy.

v. Patient has had a baseline (prior to any tumor induced osteomalacia treatment) tubular reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR) that was below the normal range for age and gender; AND
Note: Examples of tumor-induced osteomalacia treatment include Crysvita, oral phosphate/vitamin D therapy.

vi. Patient meets ONE of the following (a or b):
- **a)** Patient has tried oral phosphate and calcitriol therapy; OR

b) Per the prescriber the patient has a contraindication to oral phosphate therapy, calcitriol therapy, or both; AND

vii. The medication is prescribed by or in consultation with an endocrinologist or nephrologist.

B) Patient is Currently Receiving Crysvita. Approve for 1 year if the patient is continuing to derive benefit from Crysvita as determined by the prescriber.

Note: Examples of a response to Crysvita therapy are increased phosphorus levels, decreased symptoms of bone pain and/or muscle weakness, and increased mobility.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Crysvita is not recommended in the following situations:

1. **Chronic Kidney Disease, Severe Renal Impairment or End Stage Renal Disease**. Crysvita is contraindicated in patients with severe renal impairment or end stage renal disease.[1] These patients often have abnormal mineral metabolism which may be associated with FGF23. However, Crysvita has not been studied for the treatment of patients with chronic kidney disease who have elevations of FGF23 impacting phosphate regulation.[1,9]

2. **Epidermal Nevus Syndrome**. More data are necessary to establish the efficacy and safety of Crysvita in patients with epidermal nevus syndrome. A Phase II single-arm, open-label, dose-finding study (unpublished) included 16 adults with tumor induced osteomalacia (n = 15) or epidermal nevus syndrome (n = 1) with hypophosphatemia and an elevated FGF23.[10] Crysvita administered every 4 weeks improved mean serum phosphorus levels and increased markers of bone turnover (as measured by biopsy) at Weeks 16 and 24.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	---	04/25/2018
Annual Revision	**X-Linked Hypophosphatemia:** Added criteria for patients currently receiving Crysvita to approve if the patient is continuing to derive benefit from Crysvita as determined by the prescribing physician. Changed approval duration from 3 years to 1 year.	05/15/2019
Selected Revision	**X-Linked Hypophosphatemia:** Added criteria to allow for genetic confirmation of X-linked hypophosphatemia.	08/14/2019
Update	Date: 10/02/2019 No criteria changes. Updated overview to reflect expanded age indication.	NA
Annual Revision	**X-Linked Hypophosphatemia:** Added criteria to require patients ≥ 18 years of age to have one or more signs or symptoms of X-linked hypophosphatemia per the prescriber and to have tried oral phosphate and calcitriol therapy (or per the prescriber have a contraindication to one or both of these therapies). Wording in reference to "according to the prescribing physician" was changed to "according to the prescriber".	05/27/2020
Selected Revision	**Tumor-Induced Osteomalacia:** Added new approval criteria for this indication which include an age requirement, involvement of a specialist, the presence of signs/symptoms of tumor-induced osteomalacia, low serum phosphorus, low tubular resorption of phosphate corrected for glomerular filtration rate, and previous phosphate and calcitriol therapy. **Conditions Not Recommended for Approval:** Removed "Tumor-Induced Osteomalacia".	07/22/2020

PRIOR AUTHORIZATION POLICY

POLICY: Cushing's – Isturisa® (osilodrostat tablets – Recordati Rare Diseases)

DATE REVIEWED: 05/27/2020

OVERVIEW

Isturisa, a cortisol synthesis inhibitor, is indicated for the treatment of patients ≥ 18 years of age with Cushing's disease for whom pituitary surgery is not an option or has not been curative.[1] Isturisa inhibits cytochrome 11beta-hydroxylase, the enzyme responsible for the final step of cortisol biosynthesis in the adrenal gland. The recommended initial dose is 2 mg administered orally twice daily, with or without food. The maintenance dosage of Isturisa is individualized and determined by titration based on cortisol levels and patient's signs and symptoms. Titrate the dosage by 1 to 2 mg twice daily, no more frequently than every 2 weeks based on the rate of cortisol changes (elevated 24-hour urine free cortisol levels above upper normal limit). The maximum recommended maintenance dosage of Isturisa is 30 mg twice daily.

Disease Overview

Cushing's syndrome refers to the general state of excessive levels of cortisol (hypercortisolism) in the blood.[2,3] Hypercortisolism can occur for reasons that are either endogenous or exogenous in nature (e.g., Cushing's disease, cortisol-containing medications, adrenal gland tumor, certain cancers). The incidence of endogenous Cushing's syndrome is dependent on the population studied, ranging from 0.7 to 2.4 cases per million population per year and is more common in women than men. Endogenous Cushing's syndrome can be divided into adrenocorticotropic hormone (ACTH) -dependent and ACTH-independent with the majority of cases as ACTH-dependent (80%). Cushing's disease (hypercortisolism caused by pituitary adenomas) is the most common type of ACTH-dependent Cushing's syndrome (70%). Other ACTH-dependent causes include ectopic ACTH secretion by a benign or malignant tumor (10%) or rarely ectopic corticotropin-releasing hormone secretion by a tumor. ACTH-independent causes of

Cushing's syndrome include adrenal adenoma (10%), adrenal carcinoma (5%), adrenal hyperplasia (1% to 2%), McCune Albright syndrome (1% to 2%) and primary pigmented medullar adrenal disease, including Carney complex (1% to 2%). Patients with Cushing's syndrome exhibit a variety of signs and symptoms such as high blood pressure, diabetes, loss of libido, menstrual disorders, weight gain, hirsutism, acne, easy bruising, purplish skin striae, osteoporosis, muscle weakness, depression, and cognitive impairment as a result of prolonged and inappropriately high exposure of tissue to glucocorticoids. In patients with persistent hypercortisolism, Cushing's syndrome is accompanied by a higher mortality compared to the general population (3.8 to 5 times greater) due to vascular and metabolic comorbidities; therefore, early disease detection is important.

The role of drug therapy in patients with Cushing's syndrome is generally adjunctive and may help to improve the medical status of patients in preparation for surgery, and to control severe hypercortisolism in patients who are acutely ill, or in patients awaiting the effects of radiotherapy.[3-5] Drug therapies act at the hypothalamic-pituitary level and decrease ACTH secretion (e.g., Signifor® [pasireotide injection for subcutaneous use], Signifor® LAR [pasireotide injection for intramuscular use], bromocriptine), at the adrenal level and inhibit cortisol synthesis (steroidgenesis inhibitors [e.g., ketoconazole, Metopirone® {metyrapone capsules}, Lysodren® {mitotane tablets}, etomidate]), or at the peripheral level by competing with cortisol (Korlym® [mifepristone tablets]).[3,6] Pituitary-directed medical treatments are suggested in patients with Cushing's disease who are not surgical candidates or have persistent disease after surgery.[7] Korlym is indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.[8]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Isturisa. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Isturisa as well as the monitoring required for adverse events and long-term efficacy, approval requires Isturisa to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Isturisa is recommended in those who meet the following criteria:

FDA-Approved Indications

31. Cushing's Disease. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Isturisa is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's disease; AND
- **C)** According to the prescriber, the patient is not a candidate for surgery or surgery has not been curative.
  Note: For patients with endogenous Cushing's syndrome awaiting surgery or therapeutic response after radiotherapy, see *Other Uses with Supportive Evidence.*

Other Uses with Supportive Evidence

32. Endogenous Cushing's Syndrome. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Isturisa is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of endogenous Cushing's syndrome; AND
- **C)** According to the prescriber, the patient is not a candidate for surgery or surgery has not been curative.
  Note: For patients with endogenous Cushing's syndrome awaiting surgery or therapeutic response after radiotherapy, see *Other Uses with Supportive Evidence.*

D) The patient meets one of the following (i or ii):

i. The patient has tried one of ketoconazole tablets, Korlym® (mifepristone tablets), Metopirone® (metyrapone capsules), Lysodren® (mitotane tablets), Signifor® (pasireotide injection for subcutaneous use), or Signifor® LAR (pasireotide injection for intramuscular use) for the treatment of endogenous Cushing's syndrome; OR

ii. The patient is currently receiving Isturisa.

3. **Endogenous Cushing's Syndrome – Patients Awaiting Surgery.** Approve for 4 months if the patient meets the following criteria (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Isturisa is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's syndrome.

4. **Endogenous Cushing's Syndrome – Patients Awaiting Therapeutic Response After Radiotherapy.** Approve for 4 months if the patient meets the following criteria (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Isturisa is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's syndrome.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Isturisa not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

22. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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13. Nieman LK, Biller BM, Findling JW. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015;100(8):2807-2831.
14. Korlym™ tablets [prescribing information]. Menlo Park, CA: Corcept Pharmaceuticals; March 2020.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	05/27/2020

PRIOR AUTHORIZATION POLICY

POLICY: Cushing's – Korlym® (mifepristone 300 mg tablets – Corcept)

DATE REVIEWED: 05/27/2020

OVERVIEW

Korlym is a cortisol receptor blocker indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.[1] Korlym should not be used for the treatment of type 2 diabetes mellitus unrelated to endogenous Cushing's syndrome. Mifepristone, the active

ingredient in Korlym is also available as Mifeprex® (mifepristone 200 mg tablets) indicated for the medical termination of intrauterine pregnancy through 70 days' pregnancy.[2] Mifeprex is not included in this *Prior Authorization* policy.

Mifepristone, the active ingredient in Korlym is a selective antagonist of the progesterone receptor (PR) at low doses and blocks the glucocorticoid type 2 receptor (GR-II) at higher doses.[1] Mifepristone has high affinity for the GR-II receptor but little affinity for the GR-I (mineralocorticoid) receptor (MR). In addition, mifepristone appears to have little or no affinity for estrogen, muscarinic, histaminic, or monoamine receptors. Mifepristone acts at the receptor level to block the effects of cortisol, and its antagonistic actions affect the hypothalamic-pituitary-adrenal (HPA) axis in such a way as to further increase circulating cortisol levels while at the same time blocking their effects. Mifepristone and its three active metabolites have greater affinity for the glucocorticoid receptor (100%, 61%, 48%, and 45%, respectively) than either dexamethasone (23%) or cortisol (9%).

Cushing's Disease

Endogenous Cushing's syndrome is a rare heterogeneous disorder with diverse causes that leads to cortisol excess (hypercortisolism).[3] Patients with Cushing's syndrome exhibit a variety of signs and symptoms such as high blood pressure, diabetes, loss of libido, menstrual disorders, weight gain, hirsutism, acne, easy bruising, purplish skin striae, osteoporosis, muscle weakness, depression and cognitive impairment as a result of prolonged and inappropriately high exposure of tissue to glucocorticoids.[3-4]

The treatment of Cushing's syndrome requires a multi-modal approach. The goals of treatment are normalization of cortisol excess, long-term disease control, avoidance of recurrence and reversal of clinical features.[5] Drug therapy plays an adjunctive role in patients with Cushing's syndrome and may help to improve the medical status of patients in preparation for surgery, and to control severe hypercortisolism in patients who are acutely ill, or in patients awaiting the effects of radiotherapy.[6-9]

Medications inhibiting adrenocortical steroidgenesis (ketoconazole tablets, Metopirone® [metyrapone capsules], Lysodren® [mitotane tablets] and etomidate injection) have been widely used in patients with Cushing's syndrome of varying causes.[6] Ketoconazole tablets have a Food and Drug Administration (FDA) Orphan Drug Designation for the treatment of endogenous Cushing's syndrome.[16] Ketoconazole and metyrapone (not commercially available in the US, may be obtained from the manufacturer on a compassionate use basis) are dose-dependent and reversible inhibitors of adrenal cortisol synthesis.[6,8] Mitotane inhibits the synthesis of cortisol; however, at doses greater than 4 grams daily it causes cellular necrosis due to its irreversible effects on mitochondrial function, and therefore is primarily used in adrenal cancer.[8] Signifor is a somatostatin analog indicated for the treatment of adults with Cushing's *disease* for whom pituitary surgery is not an option or has not been curative and works by decreasing adrenocorticotropic hormone (ACTH) secretion.[13] The use of these drugs is limited by variable efficacy and adverse events (AEs).

The impairment of glucose metabolism generally resolves with normalization of cortisol levels because hypercortisolism is the causative factor for hyperglycemia.[17]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Korlym. All approvals are provided for 1 year unless otherwise noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Korlym as well as the monitoring required for AEs, approval requires Korlym to be prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's syndrome.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Korlym is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Endogenous Cushing's Syndrome.** Approve in patients who meet the following criteria (A, B, C, D and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Korlym is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's syndrome; AND
   - **C)** Korlym is being used to control hyperglycemia secondary to hypercortisolism in patients who have type 2 diabetes mellitus or glucose intolerance; AND
   - **D)** According to the prescriber, the patient is not a candidate for surgery or surgery has not been curative; AND
     Note: For patients with endogenous Cushing's syndrome awaiting surgery or therapeutic response after radiotherapy, see *Other Uses with Supportive Evidence.*
   - **E)** The patient meets one of the following (i or ii):
     - **i.** The patient has tried one of ketoconazole tablets, Metopirone (metyrapone capsules), Lysodren (mitotane tablets), or Signifor/Signifor LAR for the treatment of Cushing's syndrome; OR
     - **ii.** The patient is currently receiving Korlym.

Other Uses with Supportive Evidence

2. **Endogenous Cushing's Syndrome – Patients Awaiting Surgery.** Approve for 4 months if the patient meets the following criteria (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Korylm is prescribed by, or in consultation with, an endocrinologist or a physician who specializes in the treatment of Cushing's syndrome.

3. **Endogenous Cushing's Syndrome – Patients Awaiting Response After Radiotherapy.** Approve for 4 months if the patient meets the following criteria (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Korlym is prescribed by, or in consultation with, an endocrinologist or a physician who specializes in the treatment of Cushing's syndrome.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Korlym has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

85. **Exogenous (Iatrogenic) Cushing's Syndrome.** Korlym is not indicated in exogenous Cushing's syndrome. Exogenous Cushing's syndrome is caused by excessive glucocorticoid administration.[12] Therefore, the process to reverse the excessive cortisol exposure is to taper or discontinue the offending drug when possible.

86. Type 2 Diabetes Not Associated with Endogenous Cushing's Syndrome. Korlym should not be used for the treatment of type 2 diabetes unrelated to endogenous Cushing's syndrome.[1]

87. Psychotic Features of Psychotic Depression. Mifepristone has been used to treat the psychotic features of psychotic depression. Individual trials have demonstrated variable efficacy results.[3,10-11,15,18] In some of the studies comparing mifepristone with placebo, various statistically significant improvements in psychiatric symptoms have been noted with mifepristone relative to placebo; however, the methodology and statistical analyses of some studies have been questioned.[14] Data are inconclusive.

88. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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4. Fleseriu M, Biller BMK, Findling JW, et al. Mifepristone, a glucocorticoids receptor antagonist, produces clinical and metabolic benefits in patients with Cushing's syndrome. *J Clin Endocrin Metab*. 2012: 97(6):2039-2049.
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18. Block T, Petrides G, Kushner H, et al. Mifepristone plasma level and glucocorticoid receptor antagonism associated with response in patients with psychotic depression. *J Clin Psychopharmacol*. 2017;37(5):505-511.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual Revision	Updated policy title to include Cushing's. The requirement that Korlym be prescribed by an endocrinologist was modified to add "a physician who specializes in the treatment of Cushing's syndrome". A requirement was added to align with the FDA-approved indication to add that Korlym is being used to control hyperglycemia secondary to hypercortisolism in patients who have type 2 diabetes mellitus or glucose intolerance.	05/23/2018
Selected revision	Added Signifor LAR as option of previous therapies.	09/12/2018

Annual revision	Endogenous Cushing's Syndrome: the length of approval was updated from 3 years to 1 year. Cushing's Syndrome – Patients Awaiting Surgery: the length of approval was updated from 2 months to 4 months to align with other Cushing's policies. Created separate approval condition for Cushing's Syndrome – Patients Awaiting Therapeutic Response for Radiotherapy with a 4 month approval duration.	05/08/2019
Selected revision	**1. Endogenous Cushing's Syndrome:** The option was added as an alternative to a trial of another therapy that "The patient is currently receiving Korlym."; such patients are not subject to try another therapy prior to approval	12/18/2019
Annual revision	**Endogenous Cushing's Syndrome.** For the exception applying to patient who are not a candidate for surgery or surgery has not been curative, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). A note was added for patients with endogenous Cushing's syndrome awaiting surgery or therapeutic response after radiotherapy, see *Other Uses with Supportive Evidence.*	05/27/2020

PRIOR AUTHORIZATION POLICY

POLICY: Cushing's – Signifor™ (pasireotide injection – Novartis)

DATE REVIEWED: 05/27/2020

OVERVIEW

Signifor is an injectable cyclohexapeptide somatostatin analogue indicated for the treatment of adults with Cushing's disease for whom pituitary surgery is not an option or has not been curative.[1] Signifor exerts its pharmacological activity via binding to somatostatin receptors (ssts). Five human somatostatin receptor (hsst) subtypes are known: hsst 1, 2, 3, 4, and 5; these receptor subtypes are expressed in different tissues under normal physiological conditions. Corticotroph tumor cells from patients with Cushing's disease frequently over-express hsst 5 whereas the other receptor subtypes are often not expressed or are expressed at lower levels. Signifor binds and activates the hsst receptors resulting in inhibition of adrenocorticotropic hormone (ACTH) secretion, which leads to decreased cortisol secretion.

Signifor is administered by subcutaneous (SC) injection twice a day (BID) and the dose is titrated based on response and tolerability.[1] Patients should be evaluated for a treatment response (clinically meaningful reduction in 24-hour urinary free cortisol [UFC] levels and/or improvement in signs or symptoms of the disease) and should continue receiving therapy with Signifor as long as benefit is derived. Maximum UFC

reduction is typically seen by 2 months of treatment. Management of suspected adverse events (AEs) may require temporary dose reduction of Signifor.

Prior to the start of Signifor, patients should have baseline levels of the following: fasting plasma glucose (FPG), glycosylated hemoglobin (HbA_{1C}), liver tests and serum potassium and magnesium levels.[1] Patients should also have a baseline electrocardiogram (ECG) and gallbladder ultrasound. Treatment of patients with poorly controlled diabetes mellitus should be intensively optimized with anti-diabetic therapy prior to starting Signifor.

Cushing's Disease

Causes of endogenous Cushing's syndrome can be divided into ACTH-dependent and ACTH-independent.[2] The majority of cases of endogenous Cushing's syndrome are ACTH-dependent (80%); most of these cases are caused by pituitary adenoma (also referred to as Cushing's *disease* [70%]). Other ACTH-dependent causes include ectopic ACTH secretion by a benign or malignant tumor (10%) or rarely ectopic corticotropin-releasing hormone (CRH) secretion by a tumor. ACTH-independent causes of Cushing's syndrome include adrenal adenoma (10%), adrenal carcinoma (5%), adrenal hyperplasia (1% to 2%), McCune Albright syndrome (1% to 2%) and primary pigmented medullar adrenal disease, including Carney complex (1% to 2%).

The treatment of Cushing's syndrome requires a multi-modal approach. The goals of treatment are normalization of cortisol excess, long-term disease control, avoidance of recurrence, and reversal of clinical features.[3] In general, the initial treatment of choice for Cushing's *disease* (that is Cushing's syndrome caused by a pituitary adenoma) is selective pituitary adenomectomy by a surgeon with extensive demonstrated experience in pituitary surgery. However, the rate of cure at long-term follow-up is suboptimal and recurrences are high.[4] Immediate remission rates range from 65% to 90%, with recurrence rates reaching about 25% after 10 years.

The role of drug therapy in patients with Cushing's syndrome is generally adjunctive and may help to improve the medical status of patients in preparation for surgery, and to control severe hypercortisolism in patients who are acutely ill, or in patients awaiting the effects of radiotherapy.[2,5,6] Drug therapies act at the hypothalamic-pituitary level and decrease ACTH secretion (e.g., Signifor, bromocriptine), at the adrenal level and inhibit cortisol synthesis (steroidgenesis inhibitors [e.g., ketoconazole, Metopirone® {metyrapone capsules}, Lysodren® {mitotane tablets}, etomidate]), or at the peripheral level by competing with cortisol (Korlym® [mifepristone tablets]).[2,4] Pituitary-directed medical treatments are suggested in patients with Cushing's disease who are not surgical candidates or have persistent disease after surgery.[7]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Signifor. Because of the specialized skills required for evaluation and diagnosis of patients treated with Signifor as well as the monitoring required for AEs and long-term efficacy, approval requires Signifor to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration specified below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Signifor is recommended in those who meet the following criteria:

Food and Drug Administration (FDA)-Approved Indications

33. Cushing's Disease.

A) Initial Therapy. Approve for 4 months of initial therapy if the patient meets the following criteria (i, ii, and iii):
   i. Patient is ≥ 18 years of age; AND
   ii. Signifor is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's syndrome; AND
   iii. According to the prescriber, the patient is not a candidate for surgery or surgery has not been curative.
   Note: For patients with endogenous Cushing's syndrome awaiting surgery or therapeutic response after radiotherapy, see *Other Uses with Supportive Evidence.*

B) Patients Currently Receiving Signifor/Signifor LAR. Approve for 1 year of continuation therapy if the patient has already been started on Signifor/Signifor LAR; patient has had a response, as determined by the prescriber; and patient is continuing therapy to maintain response.

Other Uses with Supportive Evidence

2. Endogenous Cushing's Syndrome – Patients Awaiting Surgery. Approve for 4 months if the patient meets the following criteria (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Signifor is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's syndrome.

3. **Endogenous Cushing's Syndrome – Patients Awaiting Therapeutic Response After Radiotherapy.** Approve for 4 months if the patient meets the following criteria (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Signifor is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's syndrome.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Signifor has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions are provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

89. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Signifor® injection [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; January 2020.
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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual revision	Updated policy title to include Cushing's. The requirement that Signifor be prescribed by an endocrinologist was modified to add "a physician who specializes in the treatment of Cushing' syndrome".	05/23/2018
Selected revision	Added Signifor LAR to the policy under patient currently receiving therapy. Specified Cushing's Disease/"Syndrome" to approval condition and added "Patients" awaiting surgery. Approval duration increased from 2 months to 4 months to align. Created separate approval condition for Cushing's Disease/Syndrome – Patients Awaiting Therapeutic Response from Radiotherapy with 4 month approval duration. Initial therapy approval criteria for Cushing's Disease changed to 4 months.	09/12/2018
Annual revision	Removal of the following Conditions Not Recommended for Approval: Acromegaly and Neuroendocrine Tumors	05/08/2019
Annual revision	**Cushing's Disease.** For the exception applying to patient who are not a candidate for surgery or surgery has not been curative, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). The Note pertaining to patients with Cushing's disease awaiting surgery was changed to endogenous Cushing's syndrome awaiting surgery with addition of patients waiting for a therapeutic response after radiotherapy. For the exception applying to patients that have already been started on Signifor/Signifor LAR and has had a response, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). **Cushing's Disease/Syndrome – Patients Awaiting Surgery.** The condition name was changed to **Endogenous Cushing's Syndrome – Patients Awaiting Surgery**. **Cushing's Disease/Syndrome – Patients Awaiting Therapeutic Response After Radiotherapy.** The condition name was changed to **Endogenous Cushing's Syndrome – Patients Awaiting Therapeutic Response After Radiotherapy.**	05/27/2020

PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis – Bronchitol Prior Authorization Policy

- Bronchitol® (mannitol inhalation powder, for oral inhalation – Pharmaxis Ltd/Chiesi USA)

REVIEW DATE: 02/03/2021

OVERVIEW

Bronchitol, a sugar alcohol, is indicated as **add-on maintenance therapy to improve pulmonary function in patients ≥ 18 years of age with cystic fibrosis** (CF).[1]

Safety

Bronchitol can cause bronchospasm, which can be severe in susceptible patients.[1] Therefore, Bronchitol is contraindicated in individuals who fail to pass the Bronchitol Tolerance Test. Prior to prescribing Bronchitol, the Bronchitol Tolerance Test must be administered and performed under the supervision of a healthcare practitioner who is able to manage acute bronchospasm, to identify patients who are suitable candidates for Bronchitol maintenance therapy. For patients who have passed the Bronchitol Tolerance Test, the recommended dosage of Bronchitol is 400 mg twice a day (BID) by oral inhalation (the contents of 10 capsules administered individually) via the inhaler. A short-acting bronchodilator should be administered by oral inhalation, 5 to 15 minutes before every dose of Bronchitol. Bronchitol should be

taken once in the morning and once in the evening, with the later dose taken at least 2 to 3 hours before bedtime.

Guidelines

Bronchitol is not addressed in US guidelines. Guidelines from the CF Foundation (2013) in the US strongly recommend chronic use of Pulmozyme (dornase alfa inhalation solution) in patients ≥ 6 years of age with moderate to severe disease to improve lung function, quality of life, and reduce exacerbations. Pulmozyme is also recommended for chronic use in patients ≥ 6 years of age with asymptomatic or mild disease to improve lung function and reduce exacerbations. Chronic use of hypertonic saline is also recommended in individuals with CF who are ≥ 6 years of age to improve lung function and quality of life and reduce exacerbations.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Bronchitol. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Bronchitol as well as the monitoring required for adverse events and long-term efficacy, approval requires Bronchitol to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Bronchitol is recommended in those who meet the following criteria:

FDA-Approved Indications

16. Cystic Fibrosis (CF). Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has tried hypertonic saline; AND
- **C)** Patient has passed the Bronchitol Tolerance Test; AND
- **D)** Patient will pre-medicate with a short-acting bronchodilator; AND
- **E)** The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Bronchitol is not recommended in the following situations:

23. Concomitant Use with Hypertonic Saline. Bronchitol has not been studied in combination with hypertonic saline.[3-5]

24. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	02/03/2021

PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis – Kalydeco Prior Authorization Policy
- Kalydeco® (ivacaftor tablets and oral granules – Vertex)

REVIEW DATE: 02/03/2021

OVERVIEW

Kalydeco, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, is indicated for the **treatment of cystic fibrosis (CF)** in patients ≥ 4 months of age who have who have one mutation in the CFTR gene that is responsive to Kalydeco potentiation based on clinical and/or in vitro assay data.[1]

Mutations with an increase in chloride transport of 10% or greater are considered responsive. In patients with unknown genotype, a FDA-cleared CF mutation test should be used to detect the presence of the CFTR mutation followed by verification with bidirectional sequencing when recommended by the mutation test instructions for use. Kalydeco is not effective in patients with CF who are homozygous for the F508del mutation in the CFTR. A patient must have at least one CFTR mutation responsive to ivacaftor to be indicated. Table 1 lists mutations that are responsive to Kalydeco based on 1) a positive clinical response and/or 2) in vitro data in FRT cells indicating that Kalydeco increases chloride transport to ≥ 10% over baseline (% of normal).

Table 1. List of CFTR Gene Mutations that Produce CFTR Protein and are Responsive to Kalydeco.[1]

2789+5G—>A	*F311del*	*I148T*	*R75Q*	*S549N*
3272-26A—>G	*F311L*	*I175V*	*R1070Q*	*S549R*
3849+10kbC—>T	*F508C*	*I807M*	*R1070W*	*S945L*
711+3A—>G	*F508C;S1251N*	*I1027T*	*R117C*	*S977F*
A120T	*F1052V*	*I1139V*	*R117H*	*S589N*
A234D	*F1074L*	*K1060T*	*R347H*	*S737F*
A349V	*G1069R*	*L206W*	*R352Q*	*S1159F*
A1067T	*G1244E*	*L320V*	*R117G*	*S1159P*
A455E	*G1349D*	*L967S*	*R117L*	*T338I*
D110E	*G178R*	*L997F*	*R117P*	*T1053I*
D1152H	*G551D*	*L1480P*	*R170H*	*V232D*
D11OH	*G551S*	*M152V*	*R347L*	*V562I*
D192G	*G194R*	*M9521*	*R553Q*	*V754M*
D1270N	*G314E*	*M952T*	*R668C*	*V1293G*
D924N	*G576A*	*P67L*	*R792G*	*W1282R*
D579G	*G970D*	*Q237E*	*R933G*	*Y1014C*
E193K	*Y1032C*	*Q237H*	*R1162L*	*G178E*
E882K	*G1249R*	*Q359R*	*R1283M*	
E56K	*H939R*	*Q1291R*	*S1251N*	
E831X	*H1375P*	*R74W*	*S1255P*	

CFTR – Cystic fibrosis transmembrane regulator.

Guidelines

Guidelines from the CF Foundation (2018) provide guidance on the use of CFTR therapy in patients with CF, Symdeko and Trikafta are not addressed and neither is the lower pediatric age indication for Kalydeco.[2] For adults ≥ 6 years of age with CF due to a gating mutation other than G551D or R117H (e.g., G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, or G1249D), the Guidelines make a conditional recommendation for treatment with Kalydeco. For those with the R117H mutation, the Guideline panel made a conditional recommendation for treatment with Kalydeco for adults ≥ 18 years of age and for children 6 to 17 years of age with a ppFEV1 < 90%. For individuals with R117H mutation, the Guidelines recommend against treatment with Kalydeco for children 12 to 17 years of age with a percent predicted forced expiratory volume in 1 second (ppFEV1) > 90% and in children < 6 years of age.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Kalydeco. All approvals are provided for 3 years. Because of the specialized skills required for evaluation and diagnosis of patients treated with Kalydeco as well as the monitoring required for adverse events and efficacy, approval requires Kalydeco to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kalydeco is recommended in those who meet the following criteria:

FDA-Approved Indications

17. Cystic Fibrosis (CF). Approve Kalydeco for 3 years in patients who meet the following criteria (A, B, and C):

A) Patient is ≥ 4 months of age; AND

B) Patient has at least ONE of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, R347H, R352Q, A455E, D579G, S945L, S977F, F1052V, K1060T, A1067T, G1069R, R1070Q, R1070W, F1074L, D1152H, D1270N, G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D, 2789+5G—>A, 3272-26A—>G, 3849+10kbC—>T, 711+3A—>G, E831X, R117H, A120T, A234D, A349V, D192G, D924N, E882K, F311L, F311delF508C, F508C;S1251N, G178E, G194R, G314E, G576A, G970D, G1249R, H939R, H1375P, I148T, I175V, I807M, I1027T, I1139V, L320V, L967S, L997F, L1480P, M152V, M9521, M952T, Q237E, Q237H, Q359R, Q1291R, R75Q, R117G, R117L, R117P, R170H, R347L, R553Q, R668C, R792G, R933G, R1162L, R1283M, S589N, S737F, S1159F, S1159P, T338I, T1053I, V232D, V562I, V754M, V1293G, W1282R, Y1014C, or Y1032C; AND

C) The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of CF.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kalydeco is not recommended in the following situations:

1. Cystic Fibrosis (CF), Patients who are Homozygous for the phe508del (F508del) Mutation in the Cystic Fibrosis Transmembrane Regulator (CFTR) Gene. Efficacy results from a double-blind, placebo controlled trial in patients with CF who were homozygous for the phe508del mutation in the CFTR gene showed no statistically significant difference in FEV_1 over 16 weeks of Kalydeco treatment compared with placebo.[1] In a Phase II trial in patients homozygous for the F508del (n = 112) Kalydeco did not result in an improvement in FEV_1 relative to placebo.[3]

90. Cystic Fibrosis (CF), Patients with Unknown Cystic Fibrosis Transmembrane Regulator (CFTR) Gene Mutation. An FDA-cleared CF mutation test should be used to detect the presence of the CFTR mutation prior to use of Kalydeco.[1]

91. Combination Therapy with Orkambi, Symdeko, or Trikafta. Orkambi, Symdeko, and Trikafta contain ivacaftor, the active agent in Kalydeco and therefore are not indicated in combination with Kalydeco.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Added concomitant use with Symdeko to conditions not recommended for approval.	03/07/2018

Selected Revision	Update to criteria based on new FDA approved age indication to ≥ 12 months.	08/22/2018
Annual Revision	No criteria changes	03/27/2019
Selected Revision	Cystic Fibrosis (CF) approval criteria updated to reflect the new FDA indication to ≥ 6 months of age.	05/08/2019
Selected Revision	Combination Therapy with Orkambi or Symdeko: Trikafta was added to this indication not recommended for approval.	10/23/2019
Annual Revision	No criteria changes	03/25/2020
Selected Revision	Cystic Fibrosis (CF) approval criteria updated to reflect the new FDA indication to ≥ 4 months of age.	09/30/2020
Selected Revision	Cystic Fibrosis (CF): Added additional mutations to criteria for coverage (A120T, A234D, A349V, D192G, D924N, E882K, F311delF508C, F508C;S1251N, G194R, G314E, G576A, G970D, G1244E, G1249R, H939R, H1375P, I148T, I175V, I807M, I1027T, I1139V, L320V, L967S, L997F, L1480P, M152V, M9521, M952T, Q237E, Q237H, Q359R, Q1291R, R75Q, R117G, R117L, R117P, R170H, R347L, R553Q, R668C, R792G, R933G, R1162L, R1283M, S589N, S737F, S1159F, S1159P, T3381, T10531, V232D, V5621, V754M, V1293G, W1282R, Y1014C, or Y1032C).	01/06/2021
Annual Revision	Cystic Fibrosis (CF): F311L and G178E were added to the list of approvable mutations. T3381, T10531, and V5621 were amended to: T338I, T1035I, and V562I.	02/03/2021

PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis – Orkambi Prior Authorization Policy

- Orkambi™ (lumacaftor/ivacaftor tablets and oral granules – Vertex)

REVIEW DATE: 07/08/2020

OVERVIEW

Orkambi, a combination of lumacaftor and ivacaftor, is indicated for the treatment of cystic fibrosis (CF) in patients ≥ 2 years of age who are homozygous for the F508del mutation in the cystic fibrosis transmembrane regulator (CFTR) gene.[1]

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene. The efficacy and safety of Orkambi have not been established in patients with CF other than those homozygous for the F508del mutation. Orkambi contains a new chemical entity, lumacaftor, which is a CFTR corrector that increases trafficking of F508del CFTR to the cell surface, and ivacaftor (the same active ingredient contained in Kalydeco® [ivacaftor tablets and granules]), a CFTR potentiator that enhances chloride transport of CFTR on the cell surface. The F508del mutation in CFTR causes CF by limiting the amount of CFTR protein that reaches the epithelial cell surface.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Orkambi. Because of the specialized skills required for evaluation and diagnosis of patients treated with Orkambi as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Orkambi to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Orkambi is recommended in those who meet the following criteria:

FDA-Approved Indications

18. **Cystic Fibrosis (CF), Homozygous for the F508del (Phe508del) Mutation in the Cystic Fibrosis Transmembrane Regulator (CFTR) Gene.** Approve for 3 years in a patient who meets the following criteria (A, B, and C):
    A) Patient is homozygous for the F508del (Phe508del) mutation in the CFTR gene (meaning the patient has two copies of the F508del [Phe508del] mutation); AND
    B) Patient is ≥ 2 years of age; AND
    C) Orkambi is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of CF.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Orkambi is not recommended in the following situations:

25. **Cystic Fibrosis, Heterozygous for the F508del (Phe508del) Mutation in the CFTR Gene.** Orkambi is not indicated for patients with only one copy of the F508del mutation in the CFTR gene.[1] Patients who are heterozygous for the F508del mutation and have one of the following mutations are potential candidates for Kalydeco therapy: G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D, or R117H.

26. **Combination Therapy with Kalydeco, Symdeko, or Trikafta.** Orkambi contains ivacaftor, the active agent in Kalydeco and therefore is not indicated in combination with Kalydeco. Symdeko and Trikafta contain ivacaftor and are therefore not indicated in combination with Orkambi.

27. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	Added Symdeko to therapies Orkambi should not to be used in combination with.	07/11/2018
Selected revision	Added new age indication down to 2 years.	08/22/2018
Annual revision	No criteria changes.	07/10/2019
Selected revision	Combination Therapy with Kalydeco or Symdeko: Trikafta was added to this indication not recommended for approval.	10/23/2019
Annual revision	No criteria changes.	07/08/2020

PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis – Pulmozyme® (dornase alfa inhalation solution – Genentech, Inc.)

DATE REVIEWED: 05/20/2020

OVERVIEW

Pulmozyme, a recombinant human deoxyribonuclease I (rhDNase), is indicated in conjunction with standard therapies for the management of cystic fibrosis (CF) patients to improve pulmonary function.[1] According to Patient Registry data compiled by the Cystic Fibrosis Foundation (2018), Pulmozyme is used by the vast majority of patients with CF and its use continues to rise.[2]

Disease Overview

CF is an autosomal recessive disease of epithelial chloride transport estimated to affect approximately 30,000 individuals in the US.[2] Dysfunction in the cystic fibrosis transmembrane conductance regulator (CFTR) protein decreases chloride and water transport across mucus-producing cells, leading to viscous sputum.[3,4] The retained secretions allow development of chronic bronchial infection.[4] Subsequent massive neutrophil infiltration causes tissue destruction, as well as release of nucleic acids and cytosol matrix, which further contribute to mucus hyper-viscosity.[5] Pulmozyme cleaves to the extracellular DNA present in the mucus, thereby decreasing sputum viscosity.[1,4]

Guidelines

Guidelines from the CF Foundation (2007, updated in 2013) address the chronic use of medications for management of lung health in CF patients aged 6 years and older.[5,6] These guidelines recommend Pulmozyme use for CF patients regardless of disease severity to improve lung function and reduce exacerbations. Separate guidelines have addressed Pulmozyme use in younger patients.[7,8] Although efficacy data are lacking in patients under 5 years of age, safety and tolerability have been established in patients as young as 3 months.[1,8] CF Foundation guidelines for infants under 2 years of age (2009) and children between 2 and 5 years of age (2016) support Pulmozyme use in these populations based on individual circumstances.[7,8]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Pulmozyme. Because of the specialized skills required for evaluation and diagnosis of patients treated with Pulmozyme, approval requires Pulmozyme to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 3 years unless otherwise noted below.

Automation: None

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Pulmozyme is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Cystic Fibrosis.** Approve Pulmozyme for 3 years if Pulmozyme is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Pulmozyme has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Asthma.** Mucus hypersecretion may be mediated by a variety of causes, including inflammation, irritation, stimulation, or mucus-producing tumors.[9] However, efficacy of Pulmozyme is not established for conditions other than CF. In a pilot study of patients with severe acute asthma (n = 50), there was no significant difference in forced expiratory volume in 1 second (FEV_1) with Pulmozyme use vs. placebo.[10]

2. **Bronchiectasis, Idiopathic.** A multicenter, double-blind, randomized, placebo-controlled 24-week trial (n = 349) examined the effect of Pulmozyme vs. placebo on patients with idiopathic bronchiectasis (i.e., bronchiectasis not related to cystic fibrosis).[11] Patients in the Pulmozyme arm experienced worsened lung function and more frequent pulmonary exacerbations vs. placebo. The authors concluded that Pulmozyme should not be used in this population.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New policy	--	05/15/2019
Annual revision	No changes to criteria.	05/20/2020

PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis – Symdeko Prior Authorization Policy

- Symdeko® (tezacaftor/ivacaftor and ivacaftor tablets – Vertex)

REVIEW DATE: 02/03/2021

OVERVIEW

Symdeko is indicated for the **treatment of patients ≥ 6 years of age with cystic fibrosis (CF)** who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence.[1] If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use. Table 1 lists responsive CFTR mutations based on: 1) a clinical forced expiratory volume in 1 second (FEV_1) response and/or 2) *in vitro* data in FRT cells, indicating that tezacaftor/ivacaftor increases chloride transport to ≥ 10% of untreated normal over baseline. CFTR gene mutations that are not responsive to ivacaftor alone (Kalydeco®) are not expected to respond to Symdeko except for F508del homozygotes.

Table 1. List of CFTR Gene Mutations that Produce CFTR Protein and are Responsive to Symdeko.[1]

E56K	*E193K*	*S945L*	*F1074L*
P67L	*L206W*	*S977F*	*D1152H*
R74W	*R347H*	*F1052V*	*D1270N*
D110E	*R352Q*	*E831X*	*2789+5G→A*
D110H	*A455E*	*K1060T*	*3272-26A→G*
R117C	*D579G*	*A1067T*	*3849 + 10kbC→T*
*F508del**	*711+3A→G*	*R1070W*	*G622D*
A120T	*E60K*	*F1016S*	*G970D*
A234D	*E92K*	*F1099L*	*G1069R*
A349V	*E116K*	*G126D*	*G1244E*
A554E	*E403D*	*G178E*	*G1249R*
A1006E	*E558V*	*G178R*	*G1349D*
D192G	*E822K*	*G194R*	*H939R*
D443Y	*F191V*	*G194V*	*H1054D*
D443Y;G57A; R668C	*F311del*	*G314E*	*H1375P*
D614G	*F311L*	*G551D*	*I148T*
D836Y	*F508C*	*G551S*	*I175V*
D924N	*F508C;S1251N*	*G576A*	*I336K*
D979V	*F575Y*	*G576A;R668C*	*I601F*
I618T	*L346P*	*M952T*	*R74Q*
I807M	*L967S*	*P5L*	*R74W;D1270N*
I980K	*L997F*	*P205S*	*R74W;V201M*
I1027T	*L1324P*	*Q98R*	*R74W;V201M;D1270N*
I1139V	*L1335P*	*Q237E*	*R75Q*
I1269N	*L1480P*	*Q237H*	*R117G*
I1366N	*M152V*	*Q359R*	*R117H*
L15P	*M265R*	*Q1291R*	*R117L*
L320V	*M9521*	*R31L*	*R117P*

R170H	*R1066H*	*S1251N*	*W1282R*
R258G	*R1070Q*	*S1255P*	*Y109N*
R334L	*R1162L*	*T338I*	*Y161S*
R334Q	*R1283M*	*T1036N*	*Y1014C*

Table 1 (continued). List of CFTR Gene Mutations that Produce CFTR Protein and are Responsive to Symdeko.[1]

R347L	*R1283S*	*T1053I*	*Y1032C*
R347P	*S549N*	*V201M*	*R792G*
R352W	*S549R*	*V232D*	*R933G*
R553Q	*S589N*	*V562I*	*S1159F*
R668C	*S737F*	*V754M*	*S1159P*
R751L	*S912L*	*V1153E*	*V1240G*
V1293G	*546insCTA*		

CFTR – Cystic fibrosis transmembrane regulator; * A patient must have two copies of the F508del mutation or at least one copy of a responsive mutation presented in Table 1 to be indicated.

Guidelines

Guidelines from the CF Foundation (2018) provide guidance on the use of CFTR therapy in patients with CF; Symdeko is not addressed.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Symdeko. Because of the specialized skills required for evaluation and diagnosis of patients treated with Symdeko as well as the monitoring required for adverse events and efficacy, approval requires Symdeko to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 3 years unless otherwise noted below.

Automation: None

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Symdeko is recommended in those who meet the following criteria:

FDA-Approved Indications

22. Cystic Fibrosis (CF). Approve Symdeko for 3 years in patients who meet the following criteria (A, B, and C):

A) Patient meets ONE of the following conditions (i or ii):

i. Patient has at least one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, R347H, R352Q, A455E, D579G, 711+3A → G, S945L, S977F, F1052V, E831X, K1060T, A1067T, R1070W, F1074L, D1152H, D1270N, 2789+5G → A, 3272-26A → G, 3849 + 10kbC → T, 546insCTA, A120T, A234D, A349V, A554E, A1006E, D192G, D443Y, D443Y;G57A;R668C, D614G, D836Y, D924N, D979V, I618T, I807M, I980K, I1027T, I1139V, I1269N, I1366N, L15P, L320V, R170H, R258G, R334L, R334Q, R347L, R347P, R352W, R553Q, R668C, R751L, V1293G, E60K, E92K, E116K, E403D, E558V, E822K, F191V, F311del, F311L, F508C, F508C;S1251N, F575Y, L346P, L967S, L997F, L1324P, L1335P, L1480P, M152V, M265R, M9521, R1066H, R1070Q, R1162L, R1283M, R1283S, S549N, S549R, S589N, S737F, S912L, F1016S, F1099L, G126D, G178E, G178R, G194R, G194V, G314E, G551D, G551S, G576A, G576A;R668C, M952T, P5L, P205S, Q98R, Q237E, Q237H, Q359R, Q1291R, R31L, S1251N, S1255P, T338I, T1036N, T1053I, V201M, V232D, V562I, V754M, V1153E, G622D, G970D, G1069R, G1244E, G1249R, G1349D, H939R, H1054D, H1375P, I148T, I175V, I336K, I601F, R74Q, R74W;D1270N, R74W;V201M, R74W;V201M;D1270N, R75Q, R117G, R117H, R117L, R117P, W1282R, Y109N, Y161S, Y1014C, Y1032C, R792G, R933G, S1159F, S1159P, or V1240G; OR

ii. The patient has two copies of the F508del mutation; AND

B) Patient is ≥ 6 years of age; AND
C) The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of CF.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Symdeko is not recommended in the following situations:

1. **Cystic Fibrosis (CF), Patients with Unknown Cystic Fibrosis Transmembrane Regulator (CFTR) Gene Mutation.** An FDA-cleared CF mutation test should be used to detect the presence of the CFTR mutation prior to use of Symdeko[1]

92. **Combination Therapy with Orkambi, Kalydeco, or Trikafta.** Symdeko contains ivacaftor, the active agent in Kalydeco and part of Orkambi and Trikafta. Symdeko also contains tezacaftor, part of Trikafta. Symdeko is not indicated in combination with Kalydeco, Orkambi, or Trikafta.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

255. Symdeko® tablets [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; December 2020.
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258. Ren CL, Morgan RL, Oermann C, et al. Cystic Fibrosis Foundation Pulmonary Guidelines: Use of cystic fibrosis transmembrane conductance regulator modulator therapy in patients with cystic fibrosis. *Ann Am Thorac Soc*. 2018;15(3):271-280.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	Approved for FDA-approved indication	02/14/2018
Annual Revision	No criteria changes	03/06/2019
Selected Revision	Cystic Fibrosis: Criteria were modified to approve in patients ≥ 6 years of age, previously ≥ 12 years of age.	06/26/2019
Selected Revision	Combination Therapy with Orkambi or Kalydeco: Trikafta was added to this indication not recommended for approval.	10/23/2019
Annual Revision	No criteria changes	03/25/2020
Selected Revision	Cystic Fibrosis (CF): Additional mutations were added to the criteria for approval (R751L, V1293G, E60K, E92K, E116K, E403D, E558V, E822K, F191V, F311del, F311L, F508C, F508C;S1251N, F575Y, L346P, L967S, L997F, L1324P, L1335P, L1480P, M152V, M265R, M9521, R1066H, R1070Q, R1162L, R1283M, R1283S, S549N, S549R, S589N, S737F, S912L, F1016S, F1099L, G126D, G178E, G178R, G194R, G194V, G314E, G551D, G551S, G576A, G576A;R668C, M952T, P5L, P205S, Q98R, Q237E, Q237H, Q359R, Q1291R, R31L, S1251N, S1255P, T3381, T1036N, T10531, V201M, V232D, V5621, V754M, V1153E, G622D, G970D, G1069R, G1244E, G1249R, G1349D, H939R, H1054D, H1375P, I148T, I175V, I336K, I601F, R74Q, R74W;D1270N, R74W;V201M, R74W;V201M;D1270N, R75Q, R117G, R117H, R117L, R117P, W1282R, Y109N, Y161S, Y1014C, Y1032C, R792G, R933G, S1159F, S1159P, or V1240G)	01/06/2021
Annual Revision	Cystic Fibrosis (CF): T3381, T10531, and V5621 mutations were amended to T338I, T1053I, and V562I. 546insCTA was added as an approvable mutation.	02/03/2021

PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis – Trikafta Prior Authorization Policy
- Trikafta® (elexacaftor/tezacaftor/ivacaftor tablets; ivacaftor tablets, co-packaged – Vertex)

REVIEW DATE: 10/21/2020; selected revision 01/06/2021

OVERVIEW

Trikafta is a combination of ivacaftor, a cystic fibrosis transmembrane regulator (CFTR) potentiator, tezacaftor, and elexacaftor indicated for the **treatment of cystic fibrosis (CF)** in patients ≥ 12 years of age who have at least one F508del mutation in the CFTR gene or a mutation in the CFTR gene that is responsive based on *in vitro* data.[1] If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one F508del mutation. Table 1 lists responsive CFTR mutations based on *in vitro* data in Fischer Rat Thyroid cells indicating that Trikafta increases chloride transport to ≥ 10% of normal over baseline.

Table 1. List of CFTR Gene Mutations that are Responsive to Trikafta.[1]

3141del9	A349V	D110E	D579G	D1152H	G576A;R668C
E822K	F508C;S1251N	F1074L	G178E	G463V	R74W;V201M;D1270N
G1069R	H199Y	H1375P	I601F	I1139V	S492F
L967S	L1480P	M1101K	Q98R	R31L	Y563N
R117L	R334Q	R352W	R933G	R1283M	E193K
S912L	S1251N	V201M	V754M	W1098C	G622D
546insCTA	A455E	D110H	D614G	D1270N	L206W
F191V	F508del	F1099L	G178R	G480C	R75Q
G1244E	H939R	I148T	I618T	I1269N	S549N
L997F	M152V	P5L	Q237E	R74Q	Y1014C
R117P	R347H	R553Q	R1066H	R1283S	E403D
S945L	S1255P	V232D	V1153E	W1282R	G628R
A46D	A554E	D192G	D836Y	E56K	L320V
F311del	F575Y	G27R	G194R	G551D	R117C
G1249R	H1054D	I175V	I807M	I1366N	S549R
L1077P	M265R	P67L	Q237H	R74W	Y1032C
R170H	R347L	R668C	R1070Q	S13F	E474K
S977F	T338I	V456A	V1240G	Y109N	G970D
A120T	A1006E	D443Y	D924N	E60K	L346P
F311L	F1016S	G85E	G194V	G551S	R117G
G1349D	H1085P	I336K	I980K	R74W;D1270N	S589N

L1324P	M952I	P205S	Q359R	S341P	E588V
R258G	R347P	R751L	R1070W	Y161D	G1061R
S1159F	T1036N	V456F	V1293G	E92K	L453S
A234D	A1067T	D443Y;G576A;R668C	D979V	G576A	R117H
F508C	F1052V	G126D	G314E	L15P	S737F
H139R	H1085R	I502T	I1027T	R74W;V201M	L165S
L1335P	M952T	P574H	Q1291R	S364P	K1060T
R334L	R352Q	R792G	R1162L	Y161S	
S1159P	T1053I	V562I	W361R	E116K	

CFTR – Cystic Fibrosis Transmembrane Regulator.

Elexacaftor is a new chemical entity. Ivacaftor is also available as Kalydeco® (tablets and oral granules) and as part of the co-formulated Orkambi® (lumacaftor/ivacaftor tablets and oral granules).[2,3] Tezacaftor and ivacaftor are part of the co-formulated product, Symdeko® (tezacaftor/ivacaftor tablets; ivacaftor tablets).[4]

Both elexacaftor and tezacaftor bind to different sites of the CFTR protein and have an additive effect in facilitating the cellular processing and trafficking of F508del-CFTR to increase the amount of CFTR protein delivered to the cell surface compared with either molecule alone.[1] Ivacaftor potentiates the channel open probability (or gating) of the CFTR protein at the cell surface. The combined effect of the three drugs is increased quantity and function of F508del-CFTR at the cell surface, resulting in increased CFTR activity as measured by CFTR mediated chloride transport.

Guidelines

Guidelines from the CF Foundation (2018) provide guidance on the use of CFTR therapy in patients with CF; Trikafta is not addressed.[5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Trikafta. All approvals are provided for 3 years unless otherwise noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Trikafta as well as the monitoring required for adverse events and long-term efficacy, approval requires Trikafta to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Trikafta is recommended in those who meet the following criteria:

FDA-Approved Indications

19. Cystic Fibrosis (CF). Approve for 3 years if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 12 years of age; AND
- **B)** Patient has at least one copy of one of the following mutations in the cystic fibrosis conductance regulator gene: F508del, 3141del9, E822K, G1069R, L967S, R117L, S912L, 546insCTA, F191V, G1244E, L997F, R117P, S945L, A46D, F311del, G1249R, L1077P, R170H, S977F, A120T, F311L, G1349D, L1324P, R258G, S1159F, A234D, F508C, H139R, L1335P, R334L, S1159P, A349V, F508C;S1251N, H199Y, L1480P, R334Q, S1251N, A455E, H939R, M152V, R347H, S1255P, A554E, F575Y, H1054D, M265R, R347L, T338I, A1006E, F1016S, H1085P, M952I, R347P, T1036N, A1067T, F1052V, H1085R, M952T, R352Q, T1053I, D110E, F1074L, H1375P, M1101K, R352W, V201M, D110H, F1099L, I148T, P5L, R553Q, V232D, D192G, G27R, I175V, P67L, R668C, V456A, D443Y, G85E, I336K, P205S, R751L, V456F, D443Y;G576A;R668C,

G126D, I502T, P574H, R792G, V562I, D579G, G178E, I601F, Q98R, R933G, V754M, D614G, G178R, I618T, Q237E, R1066H, V1153E, D836Y, G194R, I807M, Q237H, R1070Q, V1240G, D924N, G194V, I980K, Q359R, R1070W, V1293G, D979V, G314E, I1027T, Q1291R, R1162L, W361R, D1152H, G463V, I1139V, R31L, R1283M, W1098C, D1270N, G480C, I1269N, R74Q, R1283S, W1282R, E56K, G551D, I1366N, R74W, S13F, Y109N, E60K, G551S, K1060T, R74W;D1270N, S341P, Y161D, E92K, G576A, L15P, R74W;V201M, S364P, Y161S, E116K, G576A;R668C, L165S, R74W;V201M;D1270N, S492F, Y563N, E193K, G622D, L206W, R75Q, S549N, Y1014C, E403D, G628R, L320V, R117C, S549R, Y1032C, E474K, G970D, L346P, R117G, S589N, E588V, G1061R, L453S, R117H, or S737F; AND

C) The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of CF.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Trikafta is not recommended in the following situations:

28. Cystic Fibrosis (CF), Patients with Unknown Cystic Fibrosis Transmembrane Regulator (CFTR) Gene Mutation. An FDA-cleared CF mutation test should be used to detect the presence of the CFTR mutation prior to use of Trikafta.[1]

29. Combination Therapy with Orkambi, Kalydeco, or Symdeko. Trikafta contains ivacaftor which is a component of Orkambi, Kalydeco, and Symdeko. Tezacaftor, another component of Trikafta is also contained in Symdeko.

30. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

60. Trikafta® tablets [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; December 2020.
61. Kalydeco® tablets and oral granules [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; September 2020.
62. Orkambi® tablets and oral granules [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; July 2019.
63. Symdeko® tablets [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; December 2019.
64. Ren CL, Morgan RL, Oermann C, et al. Cystic Fibrosis Foundation Pulmonary Guidelines: Use of cystic fibrosis transmembrane conductance regulator modulator therapy in patients with cystic fibrosis. *Ann Am Thorac Soc*. 2018;15(3):271-280.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/23/2019
Annual Revision	No criteria changes.	10/21/2020
Selected Revision	**Cystic Fibrosis (CF):** New mutations added to this condition of approval (3141del9, E822K, G1069R, L967S, R117L, S912L, 546insCTA, F191V, G1244E, L997F, R117P, S945L, A46D, F311del, G1249R, L1077P, R170H, S977F, A120T, F311L, G1349D, L1324P, R258G, S1159F, A234D, F508C, H139R, L1335P, R334L, S1159P, A349V, F508C;S1251N, H199Y, L1480P, R334Q, S1251N, A455E, H939R, M152V, R347H, S1255P, A554E, F575Y, H1054D, M265R, R347L, T338I, A1006E, F1016S, H1085P, M952I, R347P, T1036N, A1067T, F1052V, H1085R, M952T, R352Q, T1053I, D110E, F1074L, H1375P, M1101K, R352W, V201M, D110H, F1099L, I148T, P5L, R553Q, V232D, D192G, G27R, I175V, P67L, R668C, V456A, D443Y, G85E, I336K, P205S, R751L, V456F, D443Y;G576A;R668C, G126D, I502T, P574H, R792G, V562I, D579G, G178E, I601F, Q98R, R933G, V754M, D614G, G178R, I618T, Q237E, R1066H, V1153E, D836Y, G194R, I807M, Q237H, R1070Q, V1240G, D924N, G194V, I980K, Q359R, R1070W, V1293G, D979V, G314E, I1027T, Q1291R, R1162L, W361R,	01/06/2021

	D1152H, G463V, I1139V, R31L, R1283M, W1098C, D1270N, G480C, I1269N, R74Q, R1283S, W1282R, E56K, G551D, I1366N, R74W, S13F, Y109N, E60K, G551S, K1060T R74W;D1270N, S341P, Y161D, E92K, G576A, L15P, R74W;V201M, S364P, Y161S, E116K, G576A;R668C, L165S R74W;V201M;D1270N, S492F, Y563N, E193K, G622D, L206W, R75Q, S549N, Y1014C, E403D, G628R, L320V, R117C, S549R, Y1032C, E474K, G970D, L346P, R117G, S589N, E588V, G1061R, L453S, R117H, or S737F)	

PRIOR AUTHORIZATION POLICY

POLICY: Desmopressin Products – Nocdurna Prior Authorization Policy

- Nocdurna® (desmopressin acetate sublingual tablets [27.7 mcg and 55.3 mcg] – Ferring)

REVIEW DATE: 10/07/2020

OVERVIEW

Nocdurna, a vasopressin analog, is indicated for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least two times per night to void.[1] Before initiating therapy it is recommended that the diagnosis of nocturnal polyuria has been confirmed with a 24-hour urine collection.

Disease Overview

Nocturnal polyuria is defined as nocturnal urine volume exceeding 33% of the total 24-hour urine volume in patients ≥ 65 years of age or exceeding 20% of 24-hour urine volume in younger patients.[2] Nocturnal polyuria may improve via lifestyle and behavior modifications, which should be implemented prior to pharmacotherapy.[3] Such modifications include minimizing fluid intake before bed (particularly caffeine and alcohol), restriction of total fluid consumption, emptying the bladder before bed, increasing exercise and fitness levels, earlier dosing of medications such as diuretics, and elevating the legs above heart level for a few hours before going to bed (for patients with peripheral edema).

Safety

Nocdurna has a Boxed Warning regarding hyponatremia.[1] Use of Nocdurna is contraindicated in patients at increased risk of severe hyponatremia such as patients with excessive fluid intake, illness that may cause fluid or electrolyte imbalances, and in patients using loop diuretics or systemic or inhaled glucocorticoids. It is recommended to check serum sodium concentrations prior to initiating or resuming Nocdurna and throughout treatment. If hyponatremia occurs, Nocdurna may need to be temporarily or permanently discontinued.

Nocdurna is contraindicated in patients with hyponatremia or among those with a history of hyponatremia.[1] Also, patients with polydipsia should not use Nocdurna. Do not administer Nocdurna concomitantly with loop diuretics or with systemic or inhaled glucocorticoids. Patients with renal impairment with an estimated glomerular filtration rate below 50 mL/min/1.73 m^2 should not use Nocdurna. Those with known or suspected syndrome of inappropriate antidiuretic hormone secretion should not use Nocdurna. Do not utilize Nocdurna during illnesses that may cause fluid or electrolyte imbalance, such as gastroenteritis, salt-wasting nephropathies, or systemic infection. Nocdurna is contraindicated in patients with heart failure or among those with uncontrolled hypertension because the fluid retention in these conditions increases the risk of worsening the underlying condition. Also, Nocdurna is not recommended in patients at risk for increased intracranial pressure or those with a history of urinary retention. Trials involving Nocdurna have not included pediatric patients.

Guidelines

A consensus statement on the diagnosis and treatment of nocturia was published by the International Continence Society in 2019.[2] There was consensus that fluid restriction should be advised for all desmopressin-treated patients. Newer desmopressin formulations, including Nocdurna and Noctiva® (desmopressin acetate nasal spray), are generally regarded as low-dose desmopressin. Low-dose formulations are appropriate in the absence of contraindications to desmopressin therapy.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Nocdurna. All approvals are provided for the duration noted below. Due to the specialized skills required for evaluation and diagnosis of patients treated with Nocdurna, as well as the monitoring required for adverse events and long-term efficacy, approval requires Nocdurna to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nocdurna is recommended in those who meet the following criteria:

FDA-Approved Indications

34. Nocturia due to Nocturnal Polyuria. Approve for 1 year if the patient meets all of the following criteria (A, B, C, D, E, F, and G):

- **G)** Patient is ≥ 18 years of age; AND
- **H)** The diagnosis of nocturnal polyuria has been confirmed with a 24-hour urine collection before treatment initiation and the patient meets one of the following (i or ii):
  - **i.** The nocturnal urine volume exceeds 20% of the total 24-hour urine volume in patients < 65 years of age; OR
  - **ii.** The nocturnal urine volume exceeds 33% of the total 24-hour urine volume in patients ≥ 65 years of age; AND
- **I)** Prior to desmopressin therapy, patient awakens at least two times per night to void; AND
- **J)** Patient has serum sodium concentrations within the normal range (135 to 145 mmol/L); AND
- **K)** Prescriber has verified that the patient does not have the following conditions/circumstances in which use of Nocdurna is not recommended (i, ii, iii, iv, v, or vi):
  - **i.** Currently receiving loop diuretics (e.g., furosemide, torsemide, bumetanide); OR
  - **ii.** Currently receiving systemic or inhaled glucocorticoids; OR
  - **iii.** Renal impairment with an estimated glomerular filtration rate < 50 mL/min/1.73 m^2; OR
  - **iv.** Heart failure; OR
  - **v.** Polydipsia; OR
  - **vi.** Known or suspected syndrome of inappropriate antidiuretic hormone secretion; AND
- **L)** Patient has tried non-pharmacologic techniques or lifestyle interventions to manage the nocturia; AND

  Note: Examples of non-pharmacologic techniques include nighttime fluid restriction, avoidance of caffeine and alcohol, earlier timing of medications, leg elevation, or use of compression stockings.

- **M)** Nocdurna is prescribed by or in consultation with a urologist, geriatrician, or endocrinologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nocdurna is not recommended in the following situations:

93. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

148. Nocdurna® sublingual tablets [prescribing information]. Parsippany, NJ: Ferring Pharmaceuticals; June 2018.
149. Everaert K, Hervé F, Bosch R, et al. International Continence Society consensus on the diagnosis and treatment of nocturia. *Neurourol Urodyn*. 2019 Feb;38(2):478-498.
150. Weiss JP, Everaert K. Management of nocturia and nocturnal polyuria. *Urology*. 2019;133S:24-33.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/15/2018
Annual Revision	No changes to criteria.	09/11/2019
Annual Revision	**Nocturia due to Nocturnal Polyuria:** "Prescribing physician" was updated to "prescriber" throughout criteria. Examples of non-pharmacologic interventions were moved to a note.	10/07/2020

PRIOR AUTHORIZATION WITH STEP THERAPY POLICY

POLICY: Desmopressin Products – Noctiva Prior Authorization with Step Therapy Policy

- Noctiva™ (desmopressin acetate nasal spray for intranasal use [0.83 mcg/0.1 mL and 1.66 mcg/0.1 mL] – Avadel)

REVIEW DATE: 10/07/2020

OVERVIEW

Noctiva, a vasopressin analog, is indicated for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least two times per night to void.[1] A limitation of use is that the agent has not been studied in patients < 50 years of age.

Disease Overview

Nocturnal polyuria is defined as nocturnal urine volume exceeding 33% of the total 24-hour urine volume in patients ≥ 65 years of age or exceeding 20% of 24-hour urine volume in younger patients.[2] Nocturnal polyuria may improve via lifestyle and behavior modifications, which should be implemented prior to pharmacotherapy.[3] Such modifications include minimizing fluid intake before bed (particularly caffeine and alcohol), restriction of total fluid consumption, emptying the bladder before bed, increasing exercise and fitness levels, earlier dosing of medications such as diuretics, and elevating the legs above heart level for a few hours before going to bed (for patients with peripheral edema).

Safety

Noctiva has a Boxed Warning regarding hyponatremia.[1] Noctiva is contraindicated in patients with hyponatremia or among those with a history of hyponatremia. Also, patients with polydipsia or primary nocturnal enuresis should not use Noctiva. Do not administer Noctiva concomitantly with loop diuretics or with systemic or inhaled glucocorticoids. Patients with renal impairment with an estimated glomerular

filtration rate below 50 mL/min/1.73 m^2 should not use Noctiva. Those with known or suspected syndrome of inappropriate antidiuretic hormone secretion should not use Noctiva. Do not utilize Noctiva during illnesses that may cause fluid or electrolyte imbalance, such as gastroenteritis, salt-wasting nephropathies, or systemic infection. Noctiva is contraindicated in patients with congestive heart failure (CHF) [New York Heart Association {NYHA} class II to IV] or among those with uncontrolled hypertension because the fluid retention in these conditions increases the risk of worsening the underlying condition. Also, Noctiva is not recommended in patients at risk for increased intracranial pressure or those with a history of urinary retention, and should be used with caution (e.g., monitoring of volume status) in patients with NYHA class I CHF. Noctiva is contraindicated for the treatment of primary nocturnal enuresis because of reports of hyponatremic-related seizures in pediatric patients treated with other intranasal formulations of desmopressin. Trials involving Noctiva have not been performed in pediatric patients.

Guidelines

A consensus statement on the diagnosis and treatment of nocturia was published by the International Continence Society in 2019.[2] There was consensus that fluid restriction should be advised for all desmopressin-treated patients. Newer desmopressin formulations, including Nocdurna® (desmopressin acetate sublingual tablets [27.7 mcg and 55.3 mcg]) and Noctiva, are generally regarded as low-dose desmopressin. Low-dose formulations are appropriate in the absence of contraindications to desmopressin therapy. Oral desmopressin tablets are cited as another formulation in the consensus statement (available as 100 mcg and 200 mcg tablets in the US). This is noted to be an option for certain patients, although lower-dose formulations should be used when concomitant hyponatremia risk factors are present. Of note, it is uncertain how the pharmacokinetic profile of Noctiva aligns with the other FDA-approved nasal desmopressin products because there are no comparative bioavailability studies and Noctiva contains a novel excipient, cyclopentadecanolide, which enhances absorption.[1] The consensus statement suggests that pharmacodynamic and pharmacokinetic studies in nocturia patients during an overnight evaluation would be ideal to characterize plasma desmopressin levels and rationale for dose differentiation.[2]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Noctiva. All approvals are provided for the duration noted below. Due to the specialized skills required for evaluation and diagnosis of patients treated with Noctiva well as the monitoring required for adverse events and long-term efficacy, approval requires Noctiva to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Noctiva is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Nocturia due to Nocturnal Polyuria.** Approve for 1 year if the patient meets all of the following criteria (A, B, C, D, E, F, G and H):
   - **A)** Patient is ≥ 50 years of age; AND
   - **B)** The diagnosis of nocturnal polyuria has been confirmed with a 24-hour urine collection before treatment initiation and the patient meets one of the following (i or ii):
     - **i.** The nocturnal urine volume exceeds 20% of the total 24-hour urine volume in patients < 65 years of age; OR

ii. The nocturnal urine volume exceeds 33% of the total 24-hour urine volume in patients ≥ 65 years of age; AND

C) Prior to desmopressin therapy, patient awakens at least two times per night to void; AND

D) Patient has serum sodium concentrations within the normal range (135 to 145 mmol/L); AND

E) Prescriber has verified that the patient does not have the following conditions/circumstances in which use of Noctiva is not recommended (i, ii, iii, iv, v, or vi):

i. Currently receiving loop diuretics (e.g., furosemide, torsemide, bumetanide); OR

ii. Currently receiving systemic or inhaled glucocorticoids; OR

iii. Renal impairment with an estimated glomerular filtration rate < 50 mL/min/1.73 m^2; OR

iv. New York Heart Association class II to IV congestive heart failure; OR

v. Polydipsia; OR

vi. Known or suspected syndrome of inappropriate antidiuretic hormone secretion; AND

F) Patient has tried non-pharmacologic techniques or lifestyle interventions to manage the nocturia; AND

Note: Examples of non-pharmacologic techniques include nighttime fluid restriction, avoidance of caffeine and alcohol, earlier timing of medications, leg elevation, or use of compression stockings.

G) Patient tried one of Nocdurna (desmopressin acetate sublingual tablets) or oral desmopressin acetate tablets (DDAVP tablets, generics); AND

H) Noctiva is prescribed by or in consultation with a urologist, geriatrician, or endocrinologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Noctiva is not recommended in the following situations:

94. Primary Nocturnal Enuresis. Use of Noctiva is contraindicated for the treatment of patients with primary nocturnal enuresis.[1] Reports of hyponatremia-related seizures have occurred in pediatric patients treated with other intranasal formulations of desmopressin.

95. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Noctiva™ nasal spray [prescribing information]. Chesterfield, MO: Avadel; December 2017.
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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	-	03/07/2018
Early Annual revision	For the criteria that required that the patient has tried oral desmopressin, added Nocdurna and specified that only one product had to be tried in order to receive authorization. The title in the document was altered to include the header "desmopressin products".	08/15/2018
Annual Revision	No changes to criteria.	09/11/2019
Annual Revision	**Nocturia due to Nocturnal Polyuria:** "Prescribing physician" was updated to "prescriber" throughout criteria. Examples of non-pharmacologic interventions were moved to a note.	10/07/2020
DEU Update	**01/26/2021:** No changes to criteria. The policy was renamed to "Desmopressin Products – Noctiva Prior Authorization with Step Therapy Policy."	NA

PRIOR AUTHORIZATION POLICY

POLICY: Diabetes – Glucagon-Like Peptide-1 Agonists Prior Authorization Policy

- Adlyxin® (lixisenatide injection – sanofi-aventis)
- Bydureon® (exenatide extended-release injectable suspension – AstraZeneca)
- Bydureon BCise® (exenatide extended-release injectable suspension – AstraZeneca)
- Byetta® (exenatide injection – AstraZeneca)
- Ozempic® (semaglutide injection – Novo Nordisk)
- Rybelsus® (semaglutide tablets – Novo Nordisk)
- Tanzeum™ (albiglutide injection – GlaxoSmithKline [obsolete 07/31/2018])
- Trulicity® (dulaglutide injection – Eli Lilly)
- Victoza® (liraglutide injection – Novo Nordisk)

REVIEW DATE: 10/21/2020

OVERVIEW

The glucagon-like peptide-1 (GLP-1) receptor agonists addressed in this policy are indicated as adjuncts to diet and exercise to improve glycemic control in adults with type 2 diabetes.[1-9] Victoza is additionally indicated for type 2 diabetes in patients ≥ 10 years of age.[9] Victoza, Ozempic, and Trulicity also have labeled indications related to cardiovascular (CV) risk reduction in adults with type 2 diabetes.

Guidelines

According to the ADA Standards of Care (2020), among patients with type 2 diabetes with established atherosclerotic CV disease, sodium-glucose co-transporter 2 inhibitors or GLP-1 agonists with demonstrated CV disease benefit are recommended as part of the antihyperglycemic regimen.[10] GLP-1 agonists are also useful as add-on therapy for patients who are inadequately controlled on metformin. Other guidelines have similar recommendations.[11]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of the GLP-1 agonists targeted in this policy. Of note, Saxenda® (liraglutide injection) is indicated for weight loss, not diabetes, and is not targeted in this policy. All approvals are provided for the duration noted below.

Automation: If criteria for previous use of an oral medication for diabetes (this includes all oral medications for diabetes) in the past 130 days are not met at the point of service, coverage will be determined by prior authorization criteria.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Type 2 Diabetes Mellitus.** Approve for 3 years.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage is not recommended in the following situations:

31. **Type 1 Diabetes Mellitus.** None of the GLP-1 agonists are indicated for patients with type 1 diabetes.[1-9] Addition of GLP-1 receptor agonists to insulin therapy resulted in small (0.2%) reductions in HbA_{1C} among patients with type 1 diabetes compared with insulin alone.[10]

32. **Weight Loss Treatment**. Saxenda contains the same chemical entity as Victoza at a higher dosage and is indicated for chronic weight management. Endocrine Society guidelines for pharmacological management of obesity (2015) advise against off-label prescribing of medications such as GLP-1 receptor agonists for the sole purpose of producing weight loss.[12]

33. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Adlyxin® injection [prescribing information]. Bridgewater, NJ: sanofi-aventis; January 2019.
2. Bydureon® injectable suspension [prescribing information]. Wilmington, DE: AstraZeneca; February 2020.
3. Bydureon BCise® injectable suspension [prescribing information]. Wilmington, DE: AstraZeneca; February 2020.
4. Byetta® injection [prescribing information]. Wilmington, DE: AstraZeneca; February 2020.
5. Ozempic® injection [prescribing information]. Plainsboro, NJ: Novo Nordisk; January 2020.
6. Rybelsus® tablets [prescribing information]. Plainsboro, NJ: Novo Nordisk; January 2020.
7. Tanzeum™ injection [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; December 2017.
8. Trulicity® injection [prescribing information]. Indianapolis, IN: Eli Lilly; September 2020.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	07/10/2019
Early Annual Revision	Rybelsus added to policy. Policy statement clarified to note that Saxenda is not targeted in this policy.	10/09/2019
Annual Revision	No criteria changes.	10/21/2020

PRIOR AUTHORIZATION POLICY

POLICY: Diabetes – Symlin Prior Authorization Policy

- Symlin™ (pramlintide injection – AstraZeneca)

REVIEW DATE: 08/12/2020

OVERVIEW

Symlin, an antihyperglycemic agent for subcutaneous injection, is indicated as an adjunctive treatment in patients with type 1 or type 2 diabetes who use mealtime insulin therapy and who have failed to achieve

desired glucose control despite optimal insulin therapy.[1] Symlin is contraindicated in patients with a confirmed diagnosis of gastroparesis and in patients with hypoglycemia unawareness. At the initiation of Symlin, mealtime insulin should be decreased by 50%.

Pramlintide is a synthetic analog of the naturally occurring neuroendocrine hormone amylin which is synthesized by pancreatic β-cells and contributes to glucose control during the postprandial period.[1] Pramlintide slows gastric emptying and reduces the postprandial rise in plasma glucagon. Pramlintide has also been shown to reduce food intake via a proposed satiety mechanism.

Guidelines/Consensus Statements

The American Diabetes Association (ADA) Standards of Medical Care in Diabetes (2020) note that Symlin is the only approved treatment for adjunct therapy to insulin in type 1 diabetes; however, a specific recommendation for its use it not provided.[2] Symlin is not included on the ADA treatment algorithm for type 2 diabetes. Similarly, American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) guidelines for management of type 2 diabetes (2020) note that Symlin is approved in combination with basal-bolus insulin regimens but do not make a recommendation regarding its place in therapy.[3]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Symlin. All approvals are provided for the duration noted below.

Automation: If criteria for previous use of insulin (automated) within the past 130 days are not met at the point of service, coverage will be determined by prior authorization criteria.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Symlin is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Diabetes Mellitus, Type 1 or Type 2.** Approve for 3 years if Symlin is prescribed in adjunct to insulin therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Symlin is not recommended in the following situations:

1. **Weight Loss Treatment**. AACE/ACE obesity clinical practice guidelines (2016) comment that Symlin may lead to modest weight loss in diabetic patients but do not comment on a role for Symlin in management of obesity in non-diabetic patients.[4] Limited data are available with Symlin for weight loss treatment.[5] Other pharmacotherapies are available and indicated for weight loss.

96. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Symlin® injection [prescribing information]. Wilmington, DE: AstraZeneca; December 2019.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	No criteria changes	08/22/2018
Annual revision	No criteria changes	08/28/2019
Annual revision	No criteria changes	08/12/2020

PRIOR AUTHORIZATION POLICY

POLICY: Dronabinol Prior Authorization Policy

- Marinol® (dronabinol capsules – AbbVie, generics)
- Syndros® (dronabinol oral solution – Insys)

REVIEW DATE: 10/21/2020

OVERVIEW

Dronabinol capsules (Marinol®, generics) and Syndros® (dronabinol oral solution) are both indicated for anorexia associated with weight loss in patients with Acquired Immune Deficiency Syndrome (AIDS) and for nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.[1,2]

Dronabinol is an orally active cannabinoid which has complex effects on the central nervous system (CNS).[1,2] The active ingredient is synthetic delta-9-tetrahydrocannabinol (delta-9-THC), which is a naturally occurring component of *Cannabis sativa L.* (e.g., marijuana). Dronabinol demonstrates reversible effects on appetite, mood, cognition, memory, and perception. These effects appear to be dose-related, increasing in frequency with higher dosages, and subject to great interpatient variability. Dronabinol capsules have not been studied in and are not recommended for pediatric patients with AIDS-related anorexia; caution is recommended in prescribing dronabinol capsules for children because of the psychoactive effects. The safety and effectiveness of Syndros have not been established in pediatric patients. Dronabinol is a controlled substance; the capsules are CIII and the oral solution is CII.

In addition to the FDA-approved uses for dronabinol, several Phase III studies have been completed or are underway according to clinicaltrials.gov; the disease states being studied include anorexia nervosa, chronic pain, multiple sclerosis, and opioid dependence.[3] Published studies supporting these off-label uses are lacking.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines regarding the treatment of emesis (version 2.2020 – April 23, 2020) include various regimens depending upon the emetogenic potential of the chemotherapy agent(s) being administered.[4] Dronabinol is included in the list of medications for breakthrough nausea or emesis. Other recommended agents for breakthrough nausea or emesis include

serotonin 5-HT_3 receptor antagonists, olanzapine, lorazepam, haloperidol, metoclopramide, scopolamine, prochlorperazine, promethazine, and dexamethasone. The agent should be from a different drug class to the current regimen, but no preference is given.

Safety

Dronabinol capsules contain sesame oil and are contraindicated in patients who are allergic to this substance.[1] Syndros is contraindicated in patients with a history of hypersensitivity to alcohol and patients who are receiving, or have recently received, disulfiram- or metronidazole-containing products within 14 days.[2] Syndros contains 50% (w/w) dehydrated alcohol and 5.5% (w/w) propylene glycol.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of dronabinol. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

A. Coverage of dronabinol capsules is recommended in those who meet the following criteria:

FDA-Approved Indications

23. Anorexia Associated with Weight Loss in Patients with Acquired Immune Deficiency Syndrome (AIDS): Approve for 6 months if ONE of the following criteria is met (A or B):
- **A)** Generic dronabinol capsules are requested; OR
- **B)** If brand Marinol is prescribed, the patient has tried generic dronabinol capsules AND the Brand product is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

2. Nausea and Vomiting Associated with Cancer Chemotherapy in Patients who have Failed to Respond Adequately to Conventional Antiemetic Treatments: Approve for 1 year if the patient meets BOTH of the following criteria (A and B):
- **A)** Patient has failed to respond adequately to at least two conventional antiemetic treatments; AND
  Note: Examples of conventional antiemetic treatments include selective serotonin [5-HT_3] receptor antagonists [such as ondansetron, granisetron, Anzemet® {dolasetron}, Aloxi® {palonosetron injection}], Akynzeo® [netupitant/palonosetron capsules], Emend® (aprepitant capsules), Varubi™ (rolapitant tablets), metoclopramide, prochlorperazine, dexamethasone.
- **B)** Patient meets ONE of the following criteria (i or ii):
  - **i.** Generic dronabinol capsules are requested; OR
  - **ii.** If brand Marinol is prescribed, the patient has tried generic dronabinol capsules AND the Brand product is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

B. Coverage of Syndros is recommended in those who meet the following criteria:

FDA-Approved Indications

1. Anorexia Associated with Weight Loss in Patients with Acquired Immune Deficiency Syndrome (AIDS): Approve Syndros for 6 months if the patient meets ONE of the following criteria (A or B):
- **A)** Patient has tried generic dronabinol capsules; OR
- **B)** Patient cannot swallow or has difficulty swallowing capsules.

2. Nausea and Vomiting Associated with Cancer Chemotherapy in Patients who have Failed to Respond Adequately to Conventional Antiemetic Treatments: Approve Syndros for 1 year if the patient meets BOTH of the following criteria (A and B):
- **A)** Patient has failed to respond adequately to at least two conventional antiemetic treatments; AND

Note: Examples of conventional antiemetic treatments include selective serotonin [5-HT_3] receptor antagonists [such as ondansetron, granisetron, Anzemet® {dolasetron}, Aloxi® {palonosetron injection}], Akynzeo® [netupitant/palonosetron capsules], Emend® (aprepitant capsules), Varubi™ (rolapitant tablets), metoclopramide, prochlorperazine, dexamethasone.

B) Patient meets ONE of the following (i or ii):
- **i.** Patient has tried generic dronabinol capsules; OR
- **ii.** Patient cannot swallow or has difficulty swallowing capsules.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of dronabinol is not recommended in the following situations:

97. Chronic Non-Cancer Pain. Based on a review of published studies, there is insufficient evidence for the use of dronabinol in non-cancer pain due to the small study sizes and moderate to high risk of bias to allow for a definitive conclusion.[5] In the two studies reviewed, the authors reported mixed effects for pain measures for dronabinol. More data are needed to define the place in therapy of dronabinol in the treatment of chronic non-cancer pain.

98. Multiple Sclerosis. Results from one published, randomized, double-blind, placebo-controlled study (n = 498) demonstrated that dronabinol has no overall effect on the progression of multiple sclerosis in patients with primary and secondary progressive multiple sclerosis.[6] There is limited published evidence for the use of dronabinol in spasticity and pain in multiple sclerosis.[7-8] An analysis of three studies in patients with spasticity due to multiple sclerosis found some improvement with dronabinol vs. placebo, but it did not reach statistical significance.[7] A small study (n = 24) in patients with pain due to multiple sclerosis found that dronabinol had a modest analgesic effect, but adverse effects were also more frequent with dronabinol over placebo.[8] A study in patients with multiple sclerosis and central neuropathic pain (n = 240) found no difference between dronabinol and placebo in pain intensity.[9] More data are needed to define the place in therapy of dronabinol in the treatment of multiple sclersosis.

99. Tourette's syndrome. Published studies of dronabinol in patients with Tourette's syndrome are lacking.[10] More data are needed to define the place in therapy of dronabinol in the treatment of Tourette's syndrome.

100. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No change to criteria.	10/3/2018
Annual Revision	No change to criteria.	10/23/2019
Annual Revision	**Nausea and Vomiting Associated with Cancer Chemotherapy in Patients who have Failed to Respond Adequately to Conventional Antiemetic Treatments:** Moved examples of antiemetics to a note. Prescribing physician was changed to prescriber as needed throughout the criteria.	10/21/2020

PRIOR AUTHORIZATION POLICY

POLICY: Enspryng Prior Authorization Policy

- Enspryng™ (satralizumab-mwge for subcutaneous injection – Viela Bio)

REVIEW DATE: 08/26/2020; selected revision 09/09/2020

OVERVIEW

Enspryng, an interleukin-6 receptor antagonist, is indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in patients ≥ 18 years of age who are anti-aquaporin-4 antibody positive.[1]

Disease Overview

NMOSD is a rare, relapsing, autoimmune disorder of the brain and spinal cord with optic neuritis and/or myelitis as predominate characteristic symptoms.[2] NMOSD often causes significant, permanent damage to vision and/or spinal cord function resulting in blindness or impaired mobility.[3] Patients may experience pain, paralysis, loss of bowel and bladder control, loss of visual acuity, uncontrolled motor functions, and complications can lead to death.

Other Therapies

Soliris® (eculizumab injection for intravenous infusion) and Uplizna™ (inebilizumab-cdon injection for intravenous infusion) are two other FDA-approved medications for treatment of NMOSD in adults who are anti-AQP4 antibody-positive.[4,5] For acute attacks, typical treatment is high-dose intravenous corticosteroids.[6,7] Plasma exchange may be effective in patients who suffer acute severe attacks that do not respond to intravenous corticosteroids. For long-term control of the disease, a variety of immunosuppressive drugs are utilized as first-line therapy. Preventative maintenance therapies include corticosteroids, azathioprine, mycophenolate mofetil, and rituximab (off-label).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Enspryng. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Enspryng as well as the monitoring required for adverse events and long-term efficacy, approval requires Enspryng to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Enspryng is recommended in those who meet the following criteria:

FDA-Approved Indications

35. Neuromyelitis Optica Spectrum Disorder. Approve if the patient meets ONE of the following criteria (A or B):

C) Initial Therapy. Approve for 1 year if the patient meets the following criteria (i, ii, iii, iv, and v):

vi. Patient is ≥ 18 years of age; AND

vii. Neuromyelitis optica spectrum disorder diagnosis was confirmed by blood serum test for anti-aquaporin-4 antibody positive; AND

viii. Patient is currently receiving or has previously tried two of the following systemic therapies (a, b, c, or d):

a. Azathioprine; OR

b. Corticosteroid; OR

c. Mycophenolate mofetil; OR

d. Rituximab; AND

Note: An exception to the requirement for a trial of a systemic therapy can be made if the patient has already tried Soliris® (eculizumab injection) or Uplizna™ (inebilizumab-cdon injection) for neuromyelitis optica spectrum disorder. Patients who have already tried Soliris or Uplizna for neuromyelitis optica spectrum disorder are not required to try another systemic agent.

ix. Patient has a history of at least one relapse in the last 12 months or two relapses in the last 2 years; AND

x. The medication is being prescribed by or in consultation with a neurologist.

D) Patient is Currently Receiving Enspryng. Approve for 1 year if the patient meets the following (i, ii, iii, and iv):

v. Patient is ≥ 18 years of age; AND

vi. Neuromyelitis optica spectrum disorder diagnosis was confirmed by blood serum test for anti-aquaporin-4 antibody positive; AND

vii. According to the prescriber, patient has had clinical benefit from the use of Enspryng; AND

Note: Examples of clinical benefit include reduction in relapse rate, reduction in symptoms (e.g., pain, fatigue, motor function), and a slowing progression in symptoms.

viii. The medication is being prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Enspryng is not recommended in the following situations:

34. Concomitant use with a rituximab product, Soliris® (eculizumab injection), or Uplizna™ (inebilizumab-cdon injection). There is no evidence to support additive efficacy of combining Enspryng with rituximab, Soliris or Uplizna.

35. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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69. Uplizna™ injection [prescribing information]. Gaithersburg, MD: Viela Bio, Inc; June 2020.
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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/26/2020
Selected Revision	**Neuromyelitis Optica Spectrum Disorder.** Initial therapy approval duration was changed from 6 months to 1 year. The requirement for tried systemic therapies verbiage of "used in the maintenance setting" was removed. The addition of two relapses in the last 2 years was added as an option and (acute attack from neuromyelitis optica spectrum disorder) was removed from the history of relapses criteria. **Concomitant use with Soliris® (eculizumab injection) or Uplizna™ (inebilizumab-cdon injection).** Rituximab was added as a product not to be used concomitantly with Enspryng.	09/09/2020

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Strensiq® (asfotase alfa for subcutaneous use – Alexion Pharmaceuticals, Inc.)

TAC APPROVAL DATE: 08/08/2018

OVERVIEW

Strensiq is indicated for the treatment of patients with perinatal/infantile- and juvenile-onset hypophosphatasia (HPP).[1] Strensiq is an enzyme replacement therapy which replaces human tissue non-specific alkaline phosphatase (TNSALP). Strensiq is produced via recombinant DNA technology in Chinese hamster ovary cells. It is a soluble glycoprotein composed of two identical polypeptide chains, each containing TNSALP, bound to the Fc domain of human immunoglobulin G_1 and a deca-aspartate peptide for targeting the bone.

Disease Overview

Hypophosphatasia (HPP) is an inherited metabolic disease caused by a loss-of-function mutation in the gene which codes for TNSALP.[2] TNSALP is tissue bound and expressed in high concentrations in the liver, kidney, neurons, neutrophils, bone and teeth.[2,3] In HPP, inorganic pyrophosphate and pyridoxal 5'-phosphate, substrates for TNSALP, are increased and lead to disease manifestations. Inorganic pyrophosphate is an inhibitor of bone mineralization, and its accumulation leads to rickets and osteomalacia. Pyridoxal 5'-phosphate, a derivative of vitamin B_6, is necessary for the synthesis of gamma aminobutyric acid (GABA). However, for pyridoxal 5'-phosphate to enter the neuron, it must be dephosphorylated to allow pyridoxal to enter the neuron where it is rephosphorylated. The decreased synthesis of GABA in HPP leads to seizures.

HPP is a rare disease, with an estimated live-birth incidence, for the severe forms of HPP, of 1:100,000 in Canada and approximately 1:300,000 in Europe.[2,4] Prevalence in certain populations, such as Canadian

Mennonites may be as high as 1:2,500 births. Disease severity can range from neonatal death with almost no skeletal mineralization to dental problems in adults without any bone symptoms.[2-4] In patients most severely affected by HPP, mortality ranges from 50% to nearly 100% during infancy.[2]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Strensiq. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Strensiq as well as the monitoring required for adverse events and long-term efficacy, approval requires Strensiq to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Strensiq is recommended in those who meet the following criteria:

FDA-Approved Indications

36. Hypophosphatasia – Perinatal/Infantile- and Juvenile-Onset. Approve for 3 years if the patient meets ALL of the following criteria (A, B, C AND D):

24. Diagnosis is supported by one of the following (i, ii or iii):

- **i.** Molecular genetic testing documenting tissue non-specific alkaline phosphatase (*ALPL*) gene mutation; OR
- **ii.** Low baseline serum alkaline phosphatase activity; OR
- **iii.** An elevated level of a tissue non-specific alkaline phosphatase substrate (i.e., serum pyridoxal 5'-phosphate, serum or urinary inorganic pyrophosphate, urinary phosphoethanolamine); AND

25. Patient meets one of the following (i or ii):

- **i.** Patient currently has, or has a history of clinical manifestations consistent with hypophosphatasia (e.g., skeletal abnormalities, premature tooth loss, muscle weakness, poor feeding, failure to thrive, respiratory problems, Vitamin B_6-dependent seizures); OR
- **ii.** Patient has a family history (parent or sibling) of hypophosphatasia without current clinical manifestations of hypophosphatasia; AND

26. Disease onset ≤ 18 years of age; AND

27. Strensiq is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of hypophosphatasia or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Strensiq has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

101. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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162. White MP. Hypophosphatasia: Enzyme Replacement Therapy Brings New Opportunities and New Challenges. *J Bone Miner Res*. 2017;32:667-675.
163. Orima H. Pathophysiology of Hypophosphatasia and the Potential Role of Asfotase Alfa. *Ther Clin Risk Manag*. 2016;12:777-786.
164. Millan JL, Plotkin H. Hypophosphatasia – Pathophysiology and Treatment. *Actual Osteol*. 2012;8:164-182.

OTHER REFERENCES UTILIZED

- Whyte MP, Greenberg CR, Salman NJ, et al. Enzyme-replacement therapy in life-threatening hypophosphatasia. *N Engl J Med*. 2012;366:904-913.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
New Policy	--	08/08/2018

* For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx; TAC – Therapeutic Assessment Committee.

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Adagen Prior Authorization Policy

- Adagen® (pegademase bovine injection for intramuscular use – Leadiant [obsolete 6/30/2019])

REVIEW DATE: 11/11/2020

OVERVIEW

Adagen is a modified enzyme used for enzyme replacement therapy for the **treatment of severe combined immunodeficiency disease associated with a deficiency of adenosine deaminase (ADA-SCID).**[1] It is recommended for use in infants from birth or in children at any age at the time of diagnosis.

Disease Overview

ADA-SCID is an ultra-rare, autosomal recessive genetic disorder of purine metabolism affecting lymphocyte development, viability, and function.[1,2] It is estimated to occur in 1:200,000 to 1:1,000,000 live births. ADA is a purine salvage enzyme which metabolizes deoxyadenosine (dAdo) and adenosine (Ado) into deoxyinosine and inosine, respectively.[3] When ADA is deficient, dAdo accumulates in intracellular and extracellular compartments, along with its metabolite, deoxyadenosinetriphosphate (dATP). The buildup of both dAdo and dATP negatively impacts lymphocyte development and function by impeding DNA replication and repair, inducing apoptosis, and inhibiting lymphocyte activation.

There are a variety of phenotypes of ADA deficiency; ADA-SCID is the most severe and typically diagnosed before 1 year of age.[2] Infants with typical ADA-SCID have failure to thrive and opportunistic infections associated with marked depletion of B, T, and NK lymphocytes. Manifestations include persistent diarrhea, extensive dermatitis, recurrent pneumonia, and other life-threatening illnesses caused by opportunistic infections. Growth failure and other physical manifestations, including hepatic and neurologic abnormalities, may also be present. Without treatment, patients with ADA-SCID rarely survive beyond 1 to 2 years of age.

Guidelines

According to a consensus statement for management of ADA-SCID (2018), diagnosis is usually established by demonstrating absent or very low (< 1 % of normal) ADA catalytic activity, accompanied by elevated Ado or dAdo in plasma, urine, or dried blood spots.[4] This should be followed by genetic testing to confirm bi-allelic mutations in the *ADA* gene. Enzyme replacement therapy (ERT) is recommended by the consensus panel for all patients newly diagnosed with ADA-SCID as an immediate stabilizing measure. The ideal duration of ERT has not been established. The consensus recommends that most patients use ERT as a "bridge" for a few months to approximately 2 years prior to undergoing curative therapy with a hematopoietic stem cell transplant (HSCT) or hematopoietic stem cell gene therapy. Long-term use of ERT has declined in the past 30 years and has not been systematically studied. Lymphocyte counts and function may deteriorate over time, contributing to increased risk of infections and malignancy. Therefore, ERT longer than 5 to 8 years should be avoided and employed on a continuous basis only when neither HSCT nor gene therapy have been available or effective. The consensus also suggests ERT use for patients with later-onset phenotypes who may not be ideal candidates for curative processes.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Adagen. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Adagen, approval requires it to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Adagen is recommended in those who meet the following criteria:

FDA-Approved Indications

3. Adenosine Deaminase Severe Combined Immunodeficiency (ADA-SCID). Approve for 1 year if the patient meets the following criteria (A and B):

- **A)** Patient has a diagnosis of ADA-SCID confirmed by one of the following criteria (i or ii):
  - **i.** At baseline (i.e., prior to initiating enzyme replacement therapy), the patient has had absent or very low (< 1% of normal) adenosine deaminase (ADA) catalytic activity; OR
  - **ii.** Patient has had molecular genetic testing confirming bi-allelic mutations in the *ADA* gene; AND
- **B)** The medication is prescribed by, or in consultation with, an immunologist, hematologist/oncologist, or physician that specializes in ADA-SCID or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Adagen is not recommended in the following situations:

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

15. Adagen® [prescribing information]. Gaithersburg, MD: Leadiant Biosciences, Inc; November 2017.
16. Hershfield M. GeneReviews [Internet]. Updated March 16, 2017. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1483/. Accessed on November 2, 2020.

17. Gaspar HB, Aiuti A, Porta F, et al. How I treat ADA deficiency. *Blood*. 2009;114:3524-3532.
18. Kohn DB, Hershfield MS, Puck JM, et al. Consensus approach for the management of severe combined immune deficiency caused by adenosine deaminase deficiency. *J Allergy Clin Immunol*. 2019;143(3):852-863.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	10/31/2018
Annual Revision	No changes to criteria.	11/20/2019
Annual Revision	No changes to criteria.	11/11/2020

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Aldurazyme® (laronidase solution for intravenous infusion – Genzyme Corporation)

DATE REVIEWED: 04/15/2020

OVERVIEW

Aldurazyme is human α-L-iduronidase produced in Chinese hamster ovary cells via recombinant DNA technology.[1] Alpha-L-iduronidase catalyzes the hydrolysis of terminal α-L-iduronic acid from dermatan sulfate and heparin sulfate.

Aldurazyme is indicated for patients with Hurler and Hurler-Scheie forms of Mucopolysaccharidosis type I and in patients with the Scheie form who have moderate to severe symptoms.[1] The risks and benefits of treating mildly affected patients with the Scheie form have not been established.

Disease Overview

Mucopolysaccharidosis type I (MPS I) is a rare autosomal recessive, lysosomal storage disease characterized by the deficiency of α-L-iduronidase.[2] Patients with MPS I are unable to degrade dermatan and heparin sulfate, resulting in the accumulation of glycosoaminoglycans within lysosomes. Over time, the accumulation of glycosoaminoglycans leads to progressive tissue damage,[3] ultimately resulting in multiorgan dysfunction.[2,3] Patients with MPS I commonly have a characteristic face, corneal clouding, cardiomyopathy, enlarged tongue, respiratory insufficiency, hepatosplenomegaly, hernias, dysostosis multiplex, joint stiffness, and cognitive impairment.[4,5] MPS I is commonly classified as three separate entities, Hurler syndrome (severe form), Hurler-Scheie syndrome (intermediate form) and Scheie syndrome (mild form).[2-4] However, this classification system is based on disease severity and age of onset, not on any biochemical differences between the three syndromes.[5] All three forms of the disease are the result of the same enzymatic deficiency and represent varying degrees of severity along the disease continuum. The definitive diagnosis of MPS I is based on demonstrating deficient α-L-iduronidase activity in fibroblasts, leukocytes, plasma, or serum.[2,3,5]

Specific treatments for MPS I include hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy.[2,4,5] HSCT is indicated for the severe forms of MPS I, in children < 2 years of age who are cognitively intact.[2,4] HSCT has been shown to preserve intellectual development, reverse some aspects of somatic disease and increase survival.[2,4,5] Enzyme replacement therapy (Aldurazyme) does not cross the blood-brain barrier and is unlikely to improve cognitive or neurologic function.[2] Therefore, Aldurazyme is appropriate in children < 2 years of age who have already experienced cognitive decline, or who are cognitively intact with severe physical disease prior to HSCT to improve their health. Aldurazyme is also recommended in older patients with or without cognitive or neurologic decline.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Aldurazyme. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated

with Aldurazyme as well as the monitoring required for adverse events and long-term efficacy, approval requires Aldurazyme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Aldurazyme is recommended in those who meet the following criteria:

FDA-Approved Indications

20. Mucopolysaccharidosis Type I (Hurler Syndrome, Hurler-Scheie Syndrome, and Scheie Syndrome). Approve for 1 year if the patient meets the following criteria (A and B):

A) The diagnosis is established by one of the following (i or ii):

i. Patient has a laboratory test demonstrating deficient α-L-iduronidase activity in leukocytes, fibroblasts, plasma, or serum; OR

ii. Patient has a molecular genetic test demonstrating α-L-iduronidase gene mutation; AND

B) Aldurazyme is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Aldurazyme has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

36. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

72. Aldurazyme® solution for intravenous infusion [prescribing information]. Novato, CA: BioMarin Pharmaceutical Inc.; December 2019.
73. Muenzer J, Wraith JE, Clarke LA, et al. Mucopolysaccharidosis I: Management and treatment guidelines. *Pediatrics*. 2009;123:19-29.
74. Clarke LA, Atherton AM, Burton BK, et al. Mucopolysaccharidosis type I newborn screening: Best practices for diagnosis and management. *J Pediatr*. 2017;182:363-370.
75. Giugliani R, Federhen A, Munoz Rojas MV, et al. Mucopolysaccharidosis I, II, and VI: Brief review and guidelines for treatment. *Genet Mol Biol*. 2010;33:589-604.
76. Martins AM, Dualibi AP, Norato D, et al. Guidelines for the management of mucopolysaccharidosis type I. *J Pediatr*. 2009;155(Suppl 2):S32-S46.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/17/2019
Annual Revision	No criteria changes.	04/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Elaprase® (idursulfase injection for intravenous use – Shire Human Genetic Therapies)

DATE REVIEWED: 04/15/2020

OVERVIEW

Elaprase is human iduronate-2-sulfatase (idursulfase), produced in a human cell line using recombinant DNA technology.[1] Idursulfase hydrolyzes the 2-sulfate esters of terminal iduronate sulfate residues from dermatan and heparin sulfate in lysosomes of various cell types.

Elaprase is indicated for patients with Hunter syndrome (Mucopolysaccharidosis type II [MPS II]).[1] Elaprase has been shown to improve walking capacity in patients ≥ 5 years of age. In patients 16 months to 5 years of age, no data are available to demonstrate improvement in disease-related symptoms or long-term clinical outcome; however, treatment has reduced spleen volume similar to that of patients ≥ 5 years of age.

Disease Overview

MPS II or Hunter syndrome, is a rare, X-linked lysosomal storage disorder characterized by a deficiency of iduronate-2-sulfatase leading to the accumulation of the glycosaminoglycans dermatan sulfate and heparin sulfate.[2,3] Males are almost exclusively affected, although there have been a few case reports of females with Hunter syndrome.[3,4] The onset, progression, and severity of MPS II is variable.[2-4] Most of the patients with MPS II have a severe form with neurologic involvement leading to cognitive impairment and neurologic regression.[3,4] Other manifestations of Hunter syndrome include course facial features, hepatosplenomegaly, cardiac and respiratory disease, short stature, and stiff joints and contractures.[2,3] The definitive diagnosis of MPS II is established by demonstrating deficient iduronate-2-sulfatase activity in leukocytes, fibroblasts, serum, or plasma, or mutations in the iduronate-2-sulfatase gene.[2,5] Definitive treatment of MPS II consists of enzyme replacement therapy with Elaprase.[2-4] Hematopoietic stem cell transplantation has not demonstrated clear neurological benefit to date and is not recommended for MPS II due to the high rate of morbidity and mortality associated with this therapy.[2,4]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Elaprase. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Elaprase as well as the monitoring required for adverse events and long-term efficacy, approval requires Elaprase to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Elaprase is recommended in those who meet the following criteria:

FDA-Approved Indications

21. Mucopolysaccharidosis Type II (Hunter Syndrome). Approve for 1 year if the patient meets the following criteria (A and B):

- **A)** The diagnosis is established by one of the following (i or ii):
  - **i.** Patient has a laboratory test demonstrating deficient iduronate-2-sulfatase activity in leukocytes, fibroblasts, serum, or plasma; OR
  - **ii.** Patient has a molecular genetic test demonstrating iduronate-2-sulfatase gene mutation; AND
- **B)** Elaprase is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Elaprase has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

37. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

77. Elaprase® injection for intravenous use [prescribing information]. Lexington, MA: Shire Human Genetic Therapies, Inc.; November, 2018.
78. Scarpa M, Almassy Z, Beck M, et al. Mucopolysaccharidosis type II: European recommendations for the diagnosis and multidisciplinary management of a rare disease. *Orphanet J Rare Dis*. 2011;6:72.
79. Muenzer J, Beck M, Eng CM, et al. Multidisciplinary management of Hunter syndrome. *Pediatrics*. 2009;124:e1228-e1239.
80. Giugliani R, Federhen A, Munoz Rojas MV, et al. Mucopolysaccharidosis I, II, and VI: Brief review and guidelines for treatment. *Genet Mol Biol*. 2010;33:589-604.
81. D'Avanzo F, Rigon L, Zanetti A, Tomanin R. Mucopolysaccharidosis type II: One hundred years of research, diagnosis, and treatment. *Int J Mol Sci*. 2020;21:E1258.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/17/2019
Annual Revision	Added "serum" as a source to test to demonstrate deficient iduronate-2-sulfatase activity.	04/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Fabrazyme® (agalsidase injection for intravenous use – Genzyme)

DATE REVIEWED: 04/15/2020

OVERVIEW

Fabrazyme is human α-galactosidase A (α-Gal), with the same amino acid sequence as the native enzyme.[1] It is produced in Chinese hamster ovary cells via recombinant DNA technology. Fabrazyme catalyzes the breakdown of globotriaosylceramide (GL-3) and other α-galactyl-terminated neutral glycosphingolipids to ceramide and galactose.

Fabrazyme is indicated for use in patients with Fabry disease.[1] It reduces the deposition of GL-3 in the capillary endothelium of the kidney and certain other cell types.

Disease Overview

Fabry disease is a rare inherited X-linked lysosomal storage disorder due to absent or significantly reduced α-Gal activity leading to the accumulation of GL-3 in a wide variety of cells throughout the body.[2-4] The accumulation of GL-3 leads to progressive multisystem disease, primarily impacting the kidney, heart and nervous system.[3,4] The incidence of Fabry disease is estimated to be about 1:117,000 live male births.[2] Fabry disease can be divided into two phenotypes. A severe, classical phenotype typically occurs in men without α-Gal activity, whereas a generally milder non-classical phenotype is found in men and women with some residual α-Gal activity.[2,3] The diagnosis of Fabry disease can be confirmed in males by demonstrating a deficiency in α-Gal activity, and in all patients by identifying a Fabry disease causing gene mutation.[4] Long-term consequences of Fabry disease include hypertrophic cardiomyopathy, arrhythmias, renal failure, and stroke.[3] The kidney disease that occurs in Fabry disease is associated with progressive proteinuria and a decline in glomerular filtration rate, which over time, leads to end-stage renal disease requiring dialysis and ultimately, kidney transplantation.[2] Treatment with Fabrazyme reduces the accumulation of GL-3 in the kidney (and in other organs), with the goal of stopping or slowing the decline in kidney function.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Fabrazyme. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Fabrazyme as well as the monitoring required for adverse events and long-term efficacy, approval requires Fabrazyme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Fabrazyme is recommended in those who meet the following criteria:

FDA-Approved Indications

22. Fabry Disease. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** The diagnosis is established by one of the following (i or ii):
  - **i.** Patient has a laboratory test demonstrating deficient α-galactosidase A activity in leukocytes or fibroblasts; OR
  - **ii.** Patient has a molecular genetic test demonstrating mutations in the galactosidase alpha gene; AND
- **B)** Fabrazyme is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Fabrazyme has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

38. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

82. Fabrazyme® injection [prescribing information]. Cambridge, MA: Genzyme Corporation; December 2018.
83. Schiffmann R. Fabry Disease. *Handb Clin Neurol*. 2015;132:231-248.
84. Arends M, Wanner C, Hughes D, et al. Characterization of Classical and Nonclassical Fabry Disease: A Multinational Study. *J Am Soc Nephrol*. 2017;28:1631-1641.
85. Laney DA, Bennett RL, Clarke V, et al. Fabry Disease Practice Guidelines: Recommendations of the National Society of Genetic Counselors. *J Genet Counsel*. 2013;22:555-564.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/17/2019
Annual Revision	No criteria changes.	04/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Kanuma™ (sebelipase alfa injection for intravenous use – Alexion Pharmaceuticals)

DATE REVIEWED: 04/15/2020

OVERVIEW

Kanuma is human lysosomal acid lipase (LAL) produced in the egg white of genetically engineered chicken via recombinant DNA technology.[1] LAL catalyzes the breakdown of cholesteryl esters to free cholesterol and fatty acids, and the breakdown of triglycerides to glycerol and free fatty acids.

Kanuma is indicted for the treatment of patients with a diagnosis of LAL deficiency.[1]

Disease Overview

LAL deficiency is a rare lysosomal storage disorder characterized by absent or deficient LAL activity leading to the accumulation of cholesterol and triglycerides in the liver and other organs.[2,3] Patients with LAL deficiency often have dyslipidemias, cardiovascular disease and progressive liver disease.[2] The disorder has a heterogeneous presentation ranging from a rapidly progressive form occurring in infants which leads to death in the first year of life, to a childhood/adult-onset form with milder signs and symptoms. Almost all patients with childhood/adult-onset LAL deficiency have hepatomegaly with elevated liver transaminases and have an increased risk of developing fibrosis and cirrhosis.[3] The diagnosis of LAL deficiency is established by demonstrating deficient LAL activity in leukocytes, fibroblasts, or liver tissue, or by genetic testing.[2,3]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Kanuma. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Kanuma as well as the monitoring required for adverse events and long-term efficacy, approval requires Kanuma to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kanuma is recommended in those who meet the following criteria:

FDA-Approved Indications

23. Lysosomal Acid Lipase Deficiency. Approve for 1 year if the patient meets the following criteria (A and B):

- **A)** The diagnosis is established by one of the following (i or ii);
  - **i.** Patient has a laboratory test demonstrating deficient lysosomal acid lipase activity in leukocytes, fibroblasts, or liver tissue; OR
  - **ii.** Patient has a molecular genetic test demonstrating lysosomal acid lipase gene mutation; AND
- **B)** Kanuma is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Kanuma has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

39. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

86. Kanuma™ injection [prescribing information]. Cheshire, CT: Alexion Pharmaceuticals; December 2015.
87. Reiner Z, Guardamagna O, Nair D, et al. Lysosomal acid lipase deficiency – an under-recognized cause of dyslipidaemia and liver dysfunction. *Atherosclerosis*. 2014;235:21-30.
88. Erwin AL. The role of sebelipase alfa in the treatment of lysosomal acid lipase deficiency. *Ther Adv Gastroenterol*. 2017;10:553-562.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/17/2019
Annual Revision	No criteria changes.	04/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Lumizyme® (alglucosidase injection for intravenous use – Genzyme)

DATE REVIEWED: 04/15/2020

OVERVIEW

Lumizyme (alglucosidase) is a human hydrolytic lysosomal glycogen-specific enzyme (acid α-glucosidase) produced in Chinese hamster ovary cell line via recombinant DNA technology.[1] After administration of Lumizyme, it is internalized into cells and transported to lysosomes where it catalyzes the breakdown of glycogen to glucose.

Lumizyme is indicated for patients with Pompe disease (acid α-glucosidase deficiency).[1]

Disease Overview

Pompe disease (glycogen storage disease type II, or acid maltase deficiency), is a rare lysosomal storage disorder characterized by a deficiency in acid α-glucosidase activity leading to the accumulation of glycogen, particularly in muscle.[2,3] The onset, progression and severity of Pompe disease is variable. Infantile-onset Pompe disease usually manifests in the first few months of life and death often occurs in the first year of life and if left untreated.[2] Clinical manifestations of infantile-onset Pompe disease includes hypotonia, difficulty feeding, and cardiopulmonary failure.[4] Late-onset Pompe disease has more variable clinical course, can manifest any time after 12 months of age, and patients typically present with progressive muscle weakness which can progress to respiratory insufficiency.[3,4] The diagnosis of Pompe disease is established by demonstrating decreased acid α-glucosidase activity in blood, fibroblasts, or muscle tissue, or by genetic testing.[3,4] Definitive treatment of Pompe disease consists of enzyme replacement therapy with Lumizyme.[2-4]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Lumizyme. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lumizyme as well as the monitoring required for adverse events and long-term efficacy, approval requires Lumizyme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lumizyme is recommended in those who meet the following criteria:

FDA-Approved Indications

24. Acid Alpha-Glucosidase Deficiency (Pompe Disease). Approve for 1 year if the patient meets the following criteria (A and B):

A) The diagnosis is established by one of the following (i or ii):

i. Patient has a laboratory test demonstrating deficient acid alpha-glucosidase activity in blood, fibroblasts, or muscle tissue; OR

ii. Patient has a molecular genetic test demonstrating acid alpha-glucosidase gene mutation; AND

B) Lumizyme is prescribed by or in consultation with a geneticist, neurologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Lumizyme has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

40. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

89. Lumizyme® injection [prescribing information]. Cambridge, MA: Genzyme Corporation; February 2020.
90. Chien YH, Hwu WL, Lee NC. Pompe disease: Early diagnosis and early treatment make a difference. *Pediatr Neonatol*. 2013;54:219-227.
91. Llerena Junior JC, Nascimento OJM, Oliveira ASB, et al. Guidelines for the diagnosis, treatment and clinical monitoring of patients with juvenile and adult Pompe disease. *Arq Neuropsiquiatr*. 2016;74:166-176.
92. Cupler EJ, Berger KI, Leshner RT, et al. Consensus treatment recommendations for late-onset Pompe disease. *Muscle Nerve*. 2012;45:319-333.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/17/2019
Annual Revision	No criteria changes.	04/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Mepsevii™ (vestronidase alfa-vjbk injection, for intravenous use – Ultragenyx Pharmaceutical)

DATE REVIEWED: 04/15/2020

OVERVIEW

Mepsevii is lysosomal beta glucuronidase (GUS) produced in a Chinese hamster ovary cell line via recombinant DNA technology.[1] It has the same amino acid sequence as human GUS and catabolizes accumulated glycosaminoglycans in lysosomes in affected tissues.

Mepsevii is indicated in pediatric and adult patients for the treatment of Mucopolysaccharidosis type VII ([MPS VII], Sly syndrome).[1]

Disease Overview

MPS VII or Sly syndrome is an extremely rare lysosomal storage disorder characterized by deficient GUS activity.[2] In MPS VII, the partially catabolized glycosaminoglycans, chondroitin sulfate, dermatan sulfate, and heparin sulfate accumulate in the lysosomes, ultimately leading to the signs and symptoms of the disease.[2,3] The onset, severity and rate of progression of MPS VII is heterogeneous. Patients may present at birth with hydrops fetalis and only survive a few months while others may have milder disease and survive into their 40s.[2] However, most patients have mental retardation, hepatosplenomegaly, and musculoskeletal issues including short stature, course facial features, loss of range of motion, restricted mobility, scoliosis, and kyphosis. The diagnosis of MPS VII is established by

demonstrating deficient GUS activity in leukocytes, fibroblasts or serum, or by genetic testing.[3] Treatment for MPS VII includes enzyme replacement therapy with Mepsevii and hematopoietic stem cell transplantation.[2]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Mepsevii. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Mepsevii as well as the monitoring required for adverse events and long-term efficacy, approval requires Mepsevii to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mepsevii is recommended in those who meet the following criteria:

FDA-Approved Indications

25. Mucopolysaccharidosis Type VII (Sly Syndrome). Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** The diagnosis is established by one of the following (i or ii):
  - **i.** Patient has a laboratory test demonstrating deficient beta-glucuronidase activity in leukocytes, fibroblasts, or serum; OR
  - **ii.** Patient has a molecular genetic test demonstrating glucuronidase gene mutation; AND
- **B)** Mepsevii is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Mepsevii has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

41. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

93. Mepsevii injection [prescribing information]. Novato, CA: Ultragenyx Pharmaceutical; December 2019.
94. Montano AM, Lock-Hock N, Steiner RD, et al. Clinical course of sly syndrome (mucopolysaccharidosis type VII). *J Med Genet*. 2016;53:403-418.
95. Tomatsu S, Montano AM, Dung VC, et al. Mutations and polymorphisms in GUSB gene in mucopolysaccharidosis VII (Sly syndrome). *Hum Mutat*. 2009;30:511-519.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/17/2019
Annual Revision	No criteria changes.	04/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Naglazyme® (galsulfase injection for intravenous use – BioMarin Pharmaceuticals)

DATE REVIEWED: 04/15/2020

OVERVIEW

Naglazyme (galsulfase) is human *N*-acetylgalactosamine 4-sulfatase, produced in a Chinese hamster ovary cell line via recombinant DNA technology.[1] The enzyme catalyzes the hydrolysis of the sulfate ester from the glycosaminoglycans, chondroitin 4-sulfate and dermatan sulfate.

Naglazyme is indicated for patients with Mucopolysaccharidosis type VI (Maroteaux – Lamy syndrome [MPS VI]).[1] Naglazyme has been shown to improve walking and stair climbing capacity.

Disease Overview

MPS VI, or Maroteaux – Lamy syndrome, is a rare lysosomal storage disorder characterized by a deficiency of *N*-acetylgalactosamine 4-sulfatase (arylsulfatase B).[2,3] The enzyme deficiency results in the accumulation of partially hydrolyzed dermatan sulfate and chondroitin 4-sulfate in lysosomes leading to the signs and symptoms of the

disease.[2,3] The onset, severity and rate of progression of MPS VI is heterogeneous; however, most patients are severely affected with a rapidly progressive form.[3] Clinical manifestations include course facial features, short stature, kyphoscoliosis, joint stiffness, pulmonary insufficiency, cardiac disease, hepatosplenomegaly, corneal clouding, and hernias.[2,3] The definitive diagnosis of MPS VI is established by demonstrating deficient arylsulfatase B enzyme activity in leukocytes or fibroblasts, or by genetic testing.[2,3] Definitive treatment of MPS VI consists of either enzyme replacement therapy (ERT) with Naglazyme or hematopoietic stem cell transplantation (HSCT). Due to the morbidity and mortality associated with HSCT, this therapy is typically reserved for patients who are intolerant of or do not respond to ERT.[2]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Naglazyme. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Naglazyme as well as the monitoring required for adverse events and long-term efficacy, approval requires Naglazyme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Naglazyme is recommended in those who meet the following criteria:

FDA-Approved Indications

26. Mucopolysaccharidosis Type VI (Maroteaux – Lamy Syndrome). Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** The diagnosis is established by one of the following (i or ii):
  - **i.** Patient has a laboratory test demonstrating deficient *N*-acetylgalactosamine 4-sulfatase (arylsulfatase B) activity in leukocytes or fibroblasts; OR
  - **ii.** Patient has a molecular genetic test demonstrating arylsulfatase B gene mutation; AND
- **B)** Naglazyme is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Naglazyme has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

42. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

96. Naglazyme® injection for intravenous use [prescribing information]. Novato, CA: BioMarin Pharmaceutical, Inc.; December 2019.
97. Harmatz PR, Shediac R. Mucopolysaccharidosis VI: Pathophysiology, diagnosis and treatment. *Front Biosci*. 2017;22:385-406.
98. Vairo F, Federhen A, Baldo G, et al. Diagnostic and treatment strategies in mucopolysaccharidosis VI. *Appl Clin Genet*. 2015;8:245-255.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/17/2019
Annual Revision	No criteria changes.	04/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Revcovi Prior Authorization Policy
- Revcovi® (elapegademase-lvlr injection for intramuscular use – Leadiant)

REVIEW DATE: 11/11/2020

OVERVIEW

Revcovi is a recombinant adenosine deaminase indicated for the treatment of **adenosine deaminase severe combined immune deficiency (ADA-SCID) in pediatric and adult patients**.[1]

Disease Overview

ADA-SCID is an ultra-rare, autosomal recessive genetic disorder of purine metabolism affecting lymphocyte development, viability, and function.[1,2] It is estimated to occur in 1:200,000 to 1:1,000,000 live births. ADA is a purine salvage enzyme which metabolizes deoxyadenosine (dAdo) and adenosine (Ado) into deoxyinosine and inosine, respectively.[3] When ADA is deficient, dAdo accumulates in intracellular and extracellular compartments, along with its metabolite, deoxyadenosinetriphosphate

(dATP). The buildup of both dAdo and dATP negatively impacts lymphocyte development and function by impeding DNA replication and repair, inducing apoptosis, and inhibiting lymphocyte activation.

There are a variety of phenotypes of ADA deficiency; ADA-SCID is the most severe and typically diagnosed before 1 year of age.[2] Infants with typical ADA-SCID have failure to thrive and opportunistic infections associated with marked depletion of B, T, and NK lymphocytes. Manifestations include persistent diarrhea, extensive dermatitis, recurrent pneumonia, and other life-threatening illnesses caused by opportunistic infections. Growth failure and other physical manifestations, including hepatic and neurologic abnormalities, may also be present. Without treatment, patients with ADA-SCID rarely survive beyond 1 to 2 years of age.

Guidelines

According to a consensus statement for management of ADA-SCID (2018), diagnosis is usually established by demonstrating absent or very low (< 1 % of normal) ADA catalytic activity, accompanied by elevated Ado or dAdo in plasma, urine, or dried blood spots.[4] This should be followed by genetic testing to confirm bi-allelic mutations in the *ADA* gene. Enzyme replacement therapy (ERT) is recommended by the consensus panel for all patients newly diagnosed with ADA-SCID as an immediate stabilizing measure. The ideal duration of ERT has not been established. The consensus recommends that most patients use ERT as a "bridge" for a few months to approximately 2 years prior to undergoing curative therapy with a hematopoietic stem cell transplant (HSCT) or hematopoietic stem cell gene therapy. Long-term use of ERT has declined in the past 30 years and has not been systematically studied. Lymphocyte counts and function may deteriorate over time, contributing to increased risk of infections and malignancy. Therefore, ERT longer than 5 to 8 years should be avoided and employed on a continuous basis only when neither HSCT nor gene therapy have been available or effective. The consensus also suggests ERT use for patients with later-onset phenotypes who may not be ideal candidates for curative processes.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Revcovi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Revcovi, approval requires it to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Revcovi is recommended in those who meet the following criteria:

FDA-Approved Indications

4. **Adenosine Deaminase Severe Combined Immunodeficiency (ADA-SCID).** Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient has a diagnosis of ADA-SCID confirmed by one of the following (i or ii):
     - **i.** At baseline (i.e., prior to initiating enzyme replacement therapy), the patient has had absent or very low (< 1% of normal) adenosine deaminase (ADA) catalytic activity; OR
     - **ii.** Patient has had molecular genetic testing confirming bi-allelic mutations in the *ADA* gene; AND
   - **B)** The medication is prescribed by, or in consultation with, an immunologist, hematologist/oncologist, or physician that specializes in ADA-SCID or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Revcovi is not recommended in the following situations:

7. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

19. Revcovi® [prescribing information]. Gaithersburg, MD: Leadiant Biosciences, Inc; October 2018.
20. Hershfield M. GeneReviews [Internet]. Updated March 16, 2017. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1483/. Accessed on November 2, 2020.
21. Gaspar HB, Aiuti A, Porta F, et al. How I treat ADA deficiency. *Blood*. 2009;114:3524-3532.
22. Kohn DB, Hershfield MS, Puck JM, et al. Consensus approach for the management of severe combined immune deficiency caused by adenosine deaminase deficiency. *J Allergy Clin Immunol*. 2019;143(3):852-863.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New policy	--	10/31/2018
Annual revision	No changes to criteria.	11/20/2019
Annual Revision	No changes to criteria.	11/11/2020

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Strensiq Prior Authorization Policy

- Strensiq® (asfotase alfa for subcutaneous use – Alexion Pharmaceuticals, Inc.)

REVIEW DATE: 07/15/2020

OVERVIEW

Strensiq, a tissue non-specific alkaline phosphatase, is indicated for the treatment of patients with perinatal/infantile- and juvenile-onset hypophosphatasia (HPP).[1] Strensiq is an enzyme replacement therapy which replaces human tissue non-specific alkaline phosphatase (TNSALP).

Disease Overview

Hypophosphatasia (HPP) is an inherited metabolic disease caused by a loss-of-function mutation in the gene which codes for TNSALP.[2] TNSALP is tissue bound and expressed in high concentrations in the liver, kidney, neurons, neutrophils, bone and teeth.[2,3] In HPP, inorganic pyrophosphate and pyridoxal 5'-phosphate, substrates for TNSALP, are increased and lead to disease manifestations. Inorganic pyrophosphate is an inhibitor of bone mineralization, and its accumulation leads to rickets and osteomalacia. Pyridoxal 5'-phosphate, a derivative of vitamin B_6, is necessary for the synthesis of gamma aminobutyric acid (GABA). However, for pyridoxal 5'-phosphate to enter the neuron, it must be dephosphorylated to allow pyridoxal to enter the neuron where it is rephosphorylated. The decreased synthesis of GABA in HPP leads to seizures.

HPP is a rare disease, with an estimated live-birth incidence, for the severe forms of HPP, of 1:100,000 in Canada and approximately 1:300,000 in Europe.[2,4] Prevalence in certain populations, such as Canadian Mennonites may be as high as 1:2,500 births. Disease severity can range from neonatal death with almost no skeletal mineralization to dental problems in adults without any bone symptoms.[2-4] In patients most severely affected by HPP, mortality ranges from 50% to nearly 100% during infancy.[2]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Strensiq. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Strensiq as well as the monitoring required for adverse events and long-term efficacy, approval requires Strensiq to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Strensiq is recommended in those who meet the following criteria:

FDA-Approved Indications

37. Hypophosphatasia – Perinatal/Infantile- and Juvenile-Onset. Approve for 3 years if the patient meets all of the following criteria (A, B, C, and D):

28. Diagnosis is supported by one of the following (i, ii, or iii):

- **i.** Molecular genetic testing documenting tissue non-specific alkaline phosphatase (*ALPL*) gene mutation; OR
- **ii.** Low baseline serum alkaline phosphatase activity; OR
- **iii.** An elevated level of a tissue non-specific alkaline phosphatase substrate (i.e., serum pyridoxal 5'-phosphate, serum or urinary inorganic pyrophosphate, urinary phosphoethanolamine); AND

29. Patient meets one of the following (i or ii):

i. Patient currently has, or has a history of clinical manifestations consistent with hypophosphatasia; OR

Note: Examples of clinical manifestations include skeletal abnormalities, premature tooth loss, muscle weakness, poor feeding, failure to thrive, respiratory problems, vitamin B_6-dependent seizures.

ii. Patient has a family history (parent or sibling) of hypophosphatasia without current clinical manifestations of hypophosphatasia; AND

30. Disease onset ≤ 18 years of age; AND

31. Strensiq is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of hypophosphatasia or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Strensiq is not recommended in the following situations:

102. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

165. Strensiq® injection [prescribing information]. Cheshire, CT: Alexion Pharmaceuticals, Inc.; June, 2020.
166. Whyte MP. Hypophosphatasia: Enzyme Replacement Therapy Brings New Opportunities and New Challenges. *J Bone Miner Res*. 2017;32:667-675.
167. Orima H. Pathophysiology of Hypophosphatasia and the Potential Role of Asfotase Alfa. *Ther Clin Risk Manag*. 2016;12:777-786.
168. Millan JL, Plotkin H. Hypophosphatasia – Pathophysiology and Treatment. *Actual Osteol*. 2012;8:164-182.

OTHER REFERENCES UTILIZED

- Whyte MP, Greenberg CR, Salman NJ, et al. Enzyme-replacement therapy in life-threatening hypophosphatasia. *N Engl J Med.* 2012;366:904-913.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/08/2018
Annual review	No Criteria Changes.	07/17/2019
Annual review	No criteria changes.	07/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Sucraid® (sacrosidase oral solution – QOL Medical)

DATE REVIEWED: 04/15/2020

OVERVIEW

Sucraid is indicated as oral replacement therapy of the genetically determined sucrase deficiency, which is part of congenital sucrase-isomaltase deficiency (CSID).[1]

Disease Overview

CSID is an autosomal recessive intestinal disorder characterized by reduced or absent activity of the sucrase-isomaltase complex.[2,3] These enzymes are responsible for the hydrolysis of complex sugars and starches into simple sugars which are absorbed from the gastrointestinal tract. With absent or diminished enzyme activity, complex sugars and starches accumulate in the small intestine and lead to disease manifestations.[2] Symptoms include osmotic diarrhea, vomiting, bloating, abdominal pain, and steatorrhea.[2,3] Patients can occasionally experience dehydration, failure to thrive, developmental retardation, and muscular hypotonia.[2] The diagnosis of CSID can be established by testing small intestine biopsy specimens for reduced or absent enzyme activity, a sucrose hydrogen breath test, or by genetic testing to identify a mutation in the sucrase-isomaltase gene.[3,4]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Sucraid. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Sucraid as well as the monitoring required for adverse events and long-term efficacy, approval requires Sucraid to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sucraid is recommended in those who meet the following criteria:

FDA-Approved Indications

27. Congenital Sucrase-Isomaltase Deficiency. Approve for 1 year if the patient meets the following criteria (A and B):

- **A)** The diagnosis is established by one of the following (i, ii, or iii):
  - **i.** Patient has a laboratory test demonstrating deficient sucrase or isomaltase activity in duodenal or jejunal biopsy specimens; OR
  - **ii.** Patient has a sucrose hydrogen breath test; OR
  - **iii.** Patient has a molecular genetic test demonstrating sucrase-isomaltase mutation in saliva or blood; AND
- **B)** Sucraid is prescribed by or in consultation with a geneticist, gastroenterologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of congenital diarrheal disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Sucraid has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

43. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

99. Sucraid® oral solution [prescribing information]. Vero Beach, FL: QOL Medical; February 2019.
100. Naim HY, Heine M, Zimmer KP. Congenital sucrose-isomaltase deficiency: Heterogeneity of inheritance, trafficking, and function of an intestinal enzyme complex. *J Pediatr Gastroenterol Nutr*. 2012;55:S13-S20.
101. Cohen SA. The clinical consequences of sucrose-isomaltase deficiency. *Mol Cell Pediatr*. 2016;3:5.
102. Gericke B, Amiri M, Scott CR, Naim HY. Molecular pathogenicity of novel sucrose-isomaltase mutations found in congenital sucrose-isomaltase deficiency patients. *Biochim Biophys Acta Mol Basis Dis*. 2017;1863:817-826.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed

New Policy	--	04/17/2019
Annual Revision	No criteria changes	04/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Vimizim® (elosulfase alfa injection for intravenous use – BioMarin Pharmaceuticals)

DATE REVIEWED: 04/15/2020

OVERVIEW

Vimizim (elosulfase) is human *N*-acetylgalactosamine-6-sulfatase produced in Chinese hamster ovary cells via recombinant DNA technology.[1] Vimizim is a hydrolytic lysosomal enzyme which is taken up by lysosomes and hydrolyzes sulfate from the non-reduced ends of the glycosaminoglycans keratan sulfate and chondroitin-6-sulfate.

Vimizim is indicated for patients with Mucopolysaccharidosis type IVA (Morquio A syndrome [MPS IVA]).[1]

Disease Overview

MPS IVA (Morquio A syndrome) is a rare lysosomal storage disorder characterized by deficient *N*-acetylgalactosamine-6-sulfatase activity leading to the accumulation of chondroitin-6-sulfate and keratan sulfate in lysosomes in bone, cartilage, and ligaments.[2,3] The clinical course, onset, and severity of MPS IVA is heterogeneous.[2] Manifestations of MPS IVA include short trunk dwarfism with short neck, kyphoscoliosis, odontoid dysplasia, knock-knee, cervical spinal cord compression, hypermobile joints, cardiac disease, respiratory insufficiency, obstructive sleep apnea, corneal clouding, and dental abnormalities.[2-4] MPS IVA has not been associated with cognitive decline.[2] The definitive diagnosis of MPS IVA is established by demonstrating deficient *N*-acetylgalactosamine-6-sulfatase activity in leukocytes or fibroblasts, or by genetic testing.[2] Definitive treatment for MPS IVA consists of enzyme replacement therapy with Vimizim. Hematopoietic stem cell transplantation is not recommended for MPS IVA.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Vimizim. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vimizim as well as the monitoring required for adverse events and long-term efficacy, approval requires Vimizim to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vimizim is recommended in those who meet the following criteria:

FDA-Approved Indications

28. Mucopolysaccharidosis Type IVA (Morquio A Syndrome). Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** The diagnosis is established by one of the following (i or ii):
  - **i.** Patient has a laboratory test demonstrating deficient *N*-acetylgalactosamine-6-sulfatase activity in leukocytes or fibroblasts; OR
  - **ii.** Patient has a molecular genetic test demonstrating *N*-acetylgalactosamine-6-sulfatase gene mutation; AND
- **B)** Vimizim is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Vimizim has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

44. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

103. Vimizim® injection for intravenous use [prescribing information]. Novato, CA: BioMarin Pharmaceuticals; December 2019.
104. Hendriksz CJ, Berger KI, Giugliani R, et al. International guidelines for the management and treatment of Morquio A syndrome. *Am J Med Genet A.* 2015;167A:11-25.
105. Tomatsu S, Yasuda E, Patel P, et al. Morquio A syndrome: Diagnosis and current and future therapies. *Pediatr Endocrinol Rev.* 2014;12:141-151.
106. Regier DS, Tanpaiboon P. Role of elosulfase alfa in mucopolysaccharidosis IVA. *Appl Clin Genet*. 2016;9:67-74.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/17/2019
Annual Revision	No criteria changes.	04/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Erectile Dysfunction – Alprostadil for injection Prior Authorization Policy
- Caverject® (alprostadil for injection – Pfizer)
- Caverject Impulse® (alprostadil for injection – Pfizer)
- Edex® (alprostadil for injection – Endo Pharmaceuticals, Inc.)
- MUSE® (alprostadil urethral suppository – MEDA Pharmaceuticals)

REVIEW DATE: 9/23/2020

OVERVIEW

Injectable alprostadil products include Caverject, Caverject Impulse (disposable, single-dose, dual chamber syringe system), and Edex.[1-3] MUSE is available as a single-use, medicated transurethral system for the delivery of alprostadil directly in the urethra.[4] MUSE is administered by inserting the applicator stem into the urethra after urination. All of the alprostadil products are indicated for the treatment of ED due to

neurogenic, vasculogenic, psychogenic, or mixed etiology.[1-4] Additionally, intracavernosal Caverject may be used adjunct to other diagnostic tests in the diagnosis of ED.[1]

These products have also been studied for penile rehabilitation.[5] Alprostadil may help the recovery of erectile function by promotion of cavernosal oxygenation levels. Several studies have demonstrated the efficacy of alprostadil injections and MUSE for early penile rehabilitation post radical prostatectomy.[6-12]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of alprostadil products. Intravenous (IV) or other routes of administration of alprostadil is not covered by this policy. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with alprostadil products as well as the monitoring required for adverse events and long-term efficacy, approval requires alprostadil products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of alprostadil products are recommended in those who meet the following criteria:

FDA-Approved Indications

38. Erectile Dysfunction. Approve for 1 year.

Other Uses with Supportive Evidence

39. Prophylaxis after Radical Prostatectomy (Early Penile Rehabilitation). Approve for 1 year in treatment-naïve patients if they meet both of the following criteria (A and B).
A) Therapy will be started within 6 months of surgery; AND
B) The medication is prescribed by or in consultation with an urologist

40. Patient with a History of Radical Prostatectomy who is Continuing Alprostadil Therapy (e.g., Edex, Caverject, MUSE). Approve for 1 year if patient was started on therapy post-operatively and is currently continuing therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of alprostadil products are not recommended in the following situations:

103. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

259. Caverject® [prescribing information]. New York, NY: Pfizer; December 2017.
260. Caverject Impulse® [prescribing information]. New York, NY: Pfizer; October 2016.
261. Edex® [prescribing information]. Malvern, PA: Endo Pharmaceuticals, Inc.; July 2018.
262. MUSE [prescribing information]. Somerset, NJ: Meda Pharmaceuticals; April 2018.
263. Kim ED. Local therapies to heal the penis: Fact of fiction? *J Androl.* 2009;30:384-390.
264. Montorsi F, Guazzoni G, Strambi LF, et al. Recovery of spontaneous erectile function after nerve-sparing radical retropubic prostatectomy with and without early intracavernous injections of alprostadil: Results of a prospective, randomized trial. *J Urol.* 1997;158:1408-1410.
265. Yiou R, Cunin P, de la Taille A, et al. Sexual rehabilitation and penile pain associated with intracavernous alprostadil after radical prostatectomy. *J Sex Med.* 2011;8:575-582.
266. Raina R, Lakin MM, Thukral M, et al. Long-term efficacy and compliance of intracorporeal (IC) injection for erectile dysfunction following radical prostatectomy: SHIM (IIEF-5) analysis. *Int J Impot Res*. 2003;15(5):318-322.
267. Claro J, Aboim J, Maringolo M, et al. Intracavernous injection in the treatment of erectile dysfunction after radical prostatectomy: an observational study. *Sao Paulo Med J*. 2001;119:135-137.
268. Raina R, Pahlajani G, Agarwal A, et al. The early use of transurethral alprostadil after radical prostatectomy potentially facilitates an earlier return of erectile function and successful sexual activity. *BJU Int.* 2007;100:1317-1321.
269. Raina R, Agarwal A, Ausmundson S, et al. Long-term efficacy and compliance of MUSE for erectile dysfunction following radical prostatectomy: SHIM (IIEF-5) analysis. *Int J Impot Res.* 2005;17:86-90.
270. Raina R, Nandipati KC, Agarwal A, et al. Combination therapy: Medicated urethral system for erection enhances sexual satisfaction in sildenafil citrate failure following nerve-sparing radical prostatectomy. *J Androl.* 2005;26:757-760.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes	08/22/2018
Annual Revision	No criteria changes	08/28/2019
Annual Revision	No criteria changes	09/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Erectile Dysfunction – Sildenafil (Viagra) Prior Authorization Policy

- Viagra® (sildenafil tablets – Pfizer, generics)

REVIEW DATE: 09/23/2020

OVERVIEW

Sildenafil (Viagra, generics) are indicated for the treatment of **erectile dysfunction**.[1]

Sildenafil has been studied for other indications.

- **Pulmonary Arterial Hypertension**. Sildenafil tablets (Revatio®) are approved for pulmonary arterial hypertension.[2] Sildenafil (Viagra, generics) are available in 25 mg, 50 mg, and 100 mg tablets, and Revatio is available as 20 mg tablets. Viagra has been used for this diagnosis.[3-7] Doses of Viagra that were used in these reports ranged from 25 mg twice daily to 100 mg five times daily. Patients will have usually been started on Revatio 20 mg three times daily.
- **Raynaud Phenomenon**. Studies show Viagra has been effective in patients with Raynaud phenomenon (usually with scleroderma) who have digital ischemia, gangrene, or ulcers.[9-11] Capillary blood flow velocity increased in patients after therapy with Viagra.
- **Benign Prostatic Hyperplasia.** The European Association of Urology guidelines (2020) note that phosphodiesterase type 5 inhibitors can be used in men with moderate-to-severe lower urinary tract symptoms with or without erectile dysfunction.[13] The guidelines add that based on the results from a meta-analysis[12], younger men with lower body mass index and more severe lower urinary tract symptoms benefit the most from phosphodiesterase type 5 inhibitors.
- **Prophylaxis after Radical Prostatectomy.** Viagra given on a daily basis has been used to improve the return of normal spontaneous erectile function, improve tissue oxygenation, and prevent penile fibrosis after nerve-sparing radical prostatectomy.[14-17] It is better to initiate a penile rehabilitation program as soon as possible after surgery in order to limit and prevent postoperative local hypoxygenation and fibrosis.
- **High-Altitude Pulmonary Edema.** Published guidelines for the prevention of high-altitude pulmonary edema recommend nifedipine as the preferred pharmacologic treatment option .[18] Other pharmacologic therapies include salmeterol, tadalafil, sildenafil, dexamethasone, or acetazolamide.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of sildenafil (Viagra, generics). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with sildenafil (Viagra, generics) as well as the monitoring required for adverse events and long-term efficacy, approval requires sildenafil (Viagra, generics) to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: When available, the ICD-10 codes for male erectile dysfunction (ICD-10: N52.*) will be used for automation to allow approval of the requested medication. This automation is gender-selective and is not applicable for women; approval for use in women is always determined by prior authorization criteria.

Note: Phosphodiesterase type 5 inhibitors should not be administered, either regularly or intermittently, with concomitant nitrate therapy. Patients will be informed of the consequences should they initiate nitrate therapy while taking a phosphodiesterase type 5 inhibitor.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of sildenafil (Viagra, generics) are recommended in those who meet one of the following criteria:

FDA-Approved Indications

24. Erectile Dysfunction. Approve for 1 year.

Other Uses with Supportive Evidence

25. Pulmonary Arterial Hypertension. Approve for 1 year.

26. Raynaud's Phenomenon. Approve for 1 year if the patient meets one of the following criteria (A or B):

27. Patient has tried at least two of the following therapies for Raynaud disease: calcium channel blockers, α-adrenergic blockers, nitroglycerin, losartan, fluoxetine, or angiotensin converting enzyme (ACE) inhibitors; OR

Note: Examples of calcium channel blockers include amlodipine, felodipine, nifedipine. Examples of α-adrenergic blockers include prazosin, doxazosin. Examples of ACE inhibitors include lisinopril, benazepril, captopril, enalapril.

B) Patient has tried one vasodilator.
Note: Examples of vasodilators include: Flolan® (epoprostenol for injection), Edex® (alprostadil for injection), Tracleer® (bosentan tablets).

28. Benign Prostatic Hyperplasia. Approve for 1 year if the patient meets one of the following criteria (A or B):

29. Patient has tried an α_1-blocker; OR
Note: Examples of α_1-blockers include doxazosin, terazosin, tamsulosin, alfuzosin.

30. Patient has tried a 5α-reductase inhibitor.
Note: Examples of a 5α-reductase inhibitor includes finasteride, dutasteride.

Note: For men with erectile dysfunction and benign prostatic hyperplasia, use criterion 1 above.

5. Prophylaxis After Radical Prostatectomy (Early Penile Rehabilitation). Approve for 1 year in patients who meet the following criteria (A and B):
A) Patient had radical prostatectomy within the previous 12 months; AND
B) The medication is prescribed by or in consultation with an urologist.

6. High-Altitude Pulmonary Edema (HAPE), Treatment or Prevention. Approve for 1 year in patients who meet the following criteria (A and B):
A) Patient has HAPE or a history of HAPE; AND
B) Patient has tried one other pharmacologic therapy for the treatment or prevention of HAPE.
Note: Examples of other pharmacologic therapy for the treatment of HAPE are nifedipine, Serevent (salmeterol inhalation powder), dexamethasone, acetazolamide, Cialis (tadalafil tablets).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of sildenafil (Viagra, generics) is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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3. Garg N, Sharma MK, Sinha N. Role of oral sildenafil in severe pulmonary arterial hypertension: Clinical efficacy and dose response relationship. *Int J Cardiol.* 2007;120:306-313.
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17. Bratu O, Oprea I, Marcu D, et al. Erectile dysfunction post-radical prostatectomy- a challenge for both patient and physician. *J Med Life.* 2017;10(1):13-18.
18. Luks AM, Auerbach PS, Freer L, et al. Wilderness Medical Society Consensus Guidelines for the Prevention and Treatment of Acute Altitude Illness: 2019 Update. Available at: https://www.wemjournal.org/article/S1080-6032(19)30090-0/fulltext. Accessed on September 8, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes. Generic Viagra added.	08/22/2018
Annual Revision	No criteria changes.	08/29/2019
Annual Revision	Raynaud's Phenomenon: Moved examples of calcium channel blockers, α-adrenergic blockers, angiotensin converting enzyme inhibitors, and vasodilators to a note. Benign Prostatic Hyperplasia: Moved examples of α_1-blockers and 5α-reductase inhibitors to a note. High-Altitude Pulmonary Edema (HAPE), Treatment or Prevention: Moved other pharmacologic therapies for treatment or prevention of HAPE to a note. Removal of ICD-9 codes from automation. ICD-10 codes still applicable.	09/23/2020

PRIOR AUTHORIZATION POLICY

POLICY: Erectile Dysfunction – Stendra Prior Authorization Policy

- Stendra™ (avanafil tablets – Mist Pharmaceuticals, LLC)

REVIEW DATE: 09/23/2020

OVERVIEW

Stendra is a phosphodiesterase type 5 (PDE5) inhibitor indicated for the treatment of **erectile dysfunction** (ED).[1]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Stendra. All approvals are provided for the duration noted below.

Automation: When available, the ICD-10 codes for male erectile dysfunction (ICD-10: N52.*) will be used for automation to allow approval of the requested medication. This automation is gender-selective and is not applicable for women; approval for use in women is always determined by prior authorization criteria.

Note: Phosphodiesterase type 5 inhibitors should not be administered, either regularly or intermittently, with concomitant nitrate therapy. Patients will be informed of the consequences should they initiate nitrate therapy while taking a phosphodiesterase type 5 inhibitor.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Stendra is recommended in those who meet the following criteria:

FDA-Approved Indications

7. **Erectile Dysfunction (ED)**. Approve for 1 year.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Stendra is not recommended in the following situations:

104. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

271. Stendra™ tablets [prescribing information]. Cranford, NJ: Mist Pharmaceuticals, LLC; September 2019.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes	08/22/2018
Annual Revision	No criteria changes	8/28/2019
Annual Revision	Removal of the following Conditions Not Recommended for Approval: Benign prostatic hyperplasia and Prophylaxis of erectile dysfunction after radical prostatectomy. Removal of ICD-9 codes from automation. ICD-10 codes still applicable.	09/23/2020

PRIOR AUTHORIZATION POLICY

POLICY: Erectile Dysfunction – Tadalafil (Cialis) Prior Authorization Policy

- Cialis® (tadalafil tablets – Eli Lilly, generics)

REVIEW DATE: 09/23/2020

OVERVIEW

Tadalafil (Cialis, generics) is indicated for the following uses:

- **Erectile dysfunction**.
- **The signs and symptoms of benign prostatic hyperplasia**.
- **Erectile dysfunction and the signs and symptoms of benign prostatic hyperplasia**.

Tadalafil has been studies for other indications:

- **Raynaud phenomenon.** Multiple studies have evaluated the efficacy of tadalafil for Raynaud disease.[2-4]
- **Prophylaxis after radical prostatectomy.** Multiple studies have evaluated the efficacy of tadalafil for prophylaxis after radical prostatectomy.[5-7]
- **Pulmonary arterial hypertension.** Adcirca (and generics) contain the same active ingredient as tadalafil (Cialis, generics) and are indicated for the treatment of pulmonary arterial hypertension. Tadalafil (Cialis, generics) are available in 2.5 mg, 5 mg, 10 mg, and 20 mg tablets. Adcirca is available as a 20 mg tablet. Tadalafil (Cialis, generics) have been used in multiple studies for pulmonary arterial hypertension.[8-10]
- **High-Altitude pulmonary edema.** Published guidelines for the prevention of high-altitude pulmonary edema recommend nifedipine as the preferred pharmacologic treatment option.[11] Other pharmacologic therapies include salmeterol, sildenafil, dexamethasone, or acetazolamide.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of tadalafil (Cialis, generics). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with tadalafil (Cialis, generics) as well as the monitoring required for adverse events and long-term efficacy, approval requires tadalafil (Cialis, generics) to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: When available, the ICD-10 codes for male erectile dysfunction (ICD-10: N52.*) will be used for automation to allow approval of the requested medication. This automation is gender-selective and is not applicable for women; approval for use in women is always determined by prior authorization criteria.

Note: Phosphodiesterase type 5 inhibitors should not be administered, either regularly or intermittently, with concomitant nitrate therapy. Patients will be informed of the consequences should they initiate nitrate therapy while taking a phosphodiesterase type 5 inhibitor.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of tadalafil (Cialis, generics) are recommended in those who meet one of the following criteria:

FDA-Approved Indications

8. **Erectile Dysfunction**. Approve for 1 year.

9. **Benign Prostatic Hyperplasia.** Approve for 1 year if the patient meets one of the following criteria (A or B):
   - **A)** Patient has tried an α_1-blocker; OR
     Note: Examples of α_1-blockers include doxazosin, terazosin, tamsulosin, alfuzosin.
   - **B)** Patient has tried a 5α-reductase inhibitor.
     Note: Examples of 5α-reductase inhibitor includes finasteride, dutasteride.

   Note: For men with erectile dysfunction/benign prostatic hyperplasia, use criterion 1 above.

Other Uses with Supportive Evidence

10. **Raynaud's Phenomenon.** Approve for 1 year if the patient meets one of the following criteria (A or B):
    - **A)** Patient has tried at least two of the following therapies for Raynaud disease: calcium channel blockers, α-adrenergic blockers, nitroglycerin, losartan, fluoxetine, or angiotensin converting enzyme (ACE) inhibitors; OR
      Note: Examples of calcium channel blockers include amlodipine, felodipine, nifedipine. Examples of α-adrenergic blockers include prazosin, doxazosin. Examples of ACE inhibitors include lisiniopril, benazepril, captopril, enalapril.
    - **B)** Patient has tried one vasodilator.
      Note: Examples of vasodilators include Flolan® (epoprostenol for injection), Edex® (alprostadil for injection), Tracleer® (bosentan tablets).

4. **Prophylaxis After Radical Prostatectomy (Early Penile Rehabilitation).** Approve for 1 year in patients who meet the following criteria (A and B):
   A) Patient had radical prostatectomy within the previous 12 months; AND
   B) The medication is prescribed by or in consultation with an urologist.

5. **Pulmonary Arterial Hypertension (PAH).** Approve for 1 year in patients who cannot use Adcirca (or generics of Adcirca) because the dose is not available using Adcirca (or generics of Adcirca), that is, patients who are using 10 mg doses of tadalafil (Cialis, generics).
   Note: Patients using 20 mg or 40 mg of tadalafil (Cialis, generics) for PAH should use Adcirca (or generics of Adcirca).

6. **High-Altitude Pulmonary Edema (HAPE), Treatment or Prevention**. Approve for 1 year in patients who meet the following criteria (A and B):
   A) Patient has HAPE or a history of HAPE; AND
   B) Patient has tried one other pharmacologic therapy for treatment or prevention of HAPE.
   Note: Examples of other pharmacologic therapy for the treatment of HAPE are nifedipine, Serevent (salmeterol inhalation powder), dexamethasone, acetazolamide, Viagra (sildenafil).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of tadalafil (Cialis, generics) is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes	08/22/2018
Annual Revision	Generic Cialis was added to policy. Criteria specific to Pulmonary Arterial Hypertension (PAH) was updated to include generic Adcirca.	08/28/2019
Annual Revision	Benign Prostatic Hyperplasia: Moved examples of α_1-blockers and 5α-reductase inhibitors to a note. Raynaud's Phenomenon: Moved examples of calcium channel blockers, α-adrenergic blockers, angiotensin converting enzyme inhibitors, and vasodilators to a note. High-Altitude Pulmonary Edema (HAPE), Treatment or Prevention: Moved other pharmacologic therapies for treatment or prevention of HAPE to a note. Removal of ICD-9 codes from automation. ICD-10 codes still applicable.	09/23/2020

PRIOR AUTHORIZATION POLICY

POLICY: Erectile Dysfunction – Vardenafil (Levitra, Staxyn) Prior Authorization Policy

- Levitra® (vardenafil tablets – GlaxoSmithKline, generics)
- Staxyn™ (vardenafil orally disintegrating tablet – GlaxoSmithKline, generics)

REVIEW DATE: 09/23/2020

OVERVIEW

Vardenafil (Levitra, generics) and vardenafil orally disintegrating tablets (Staxyn, generics) are indicated for the treatment of **erectile dysfunction**.[1,2]

Vardenafil has been studied for other indications:

- **Raynaud Phenomenon**. Vardenafil has been studied in patients with Raynaud phenomenon.[3,4] Levitra improved digital blood flow and decreased the number of Raynaud's attacks.
- **Benign Prostatic Hyperplasia**. Vardenafil has been studied in benign prostatic hyperplasia.[5,6] The European Association of Urology guidelines (2020) note that phosphodiesterase type 5 inhibitors can be used in men with moderate-to-severe lower urinary tract symptoms with or without erectile dysfunction.[7] The guidelines add that based on the results from a meta-analysis[8], younger men with lower body mass index and more severe lower urinary tract symptoms benefits the most from phosphodiesterase type 5 inhibitors.
- **Prophylaxis after Radical Prostatectomy**. Vardenafil was studied in men following bilateral nerve-sparing radical prostatectomy.[9]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of vardenafil tablets (Levitra, generics) and vardenafil orally disintegrating tablets (Staxyn, generics). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with vardenafil tablets (Levitra, generics) and vardenafil orally disintegrating tablets (Staxyn, generics) as well as the monitoring required for adverse events and long-term efficacy, approval requires vardenafil tablets (Levitra, generics) and vardenafil orally disintegrating tablets (Staxyn, generics) to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: When available, the ICD-10 codes for male erectile dysfunction (ICD-10: N52.*) will be used for automation to allow approval of the requested medication. This automation is gender-selective and is not applicable for women; approval for use in women is always determined by prior authorization criteria.

Note: Phosphodiesterase type 5 inhibitors should not be administered, either regularly or intermittently, with concomitant nitrate therapy. Patients will be informed of the consequences should they initiate nitrate therapy while taking a phosphodiesterase type 5 inhibitor.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of vardenafil tablets (Levitra, generics) or vardenafil orally disintegrating tablet (Staxyn, generics) is recommended in those who meet one of the following criteria:

FDA-Approved Indications

11. Erectile Dysfunction. Approve for 1 year.

Other Uses with Supportive Evidence

2. Raynaud's Phenomenon. Approve for 1 year if the patient meets one of the following criteria (A or B):

A) Patient has tried at least two of the following therapies: calcium channel blockers, α-adrenergic blockers, nitroglycerin, losartan fluoxetine, or angiotensin converting enzyme (ACE) inhibitors; OR

Note: Examples of calcium channel blockers include amlodipine, felodipine, nifedipine. Examples of α-adrenergic blockers include prazosin, doxazosin. Examples of ACE inhibitors include lisinopril, benazepril, captopril, enalapril.

B) Patient has tried one vasodilator.

Note: Examples of vasodilators include Flolan® (epoprostenol for injection), Edex® (alprostadil for injection), Tracleer® (bosentan tablets).

3. Benign Prostatic Hyperplasia. Approve for 1 year if the patient meets one of the following criteria (A or B):

A) Patient has tried an α_1-blocker; OR

Note: Examples of α_1-blockers include doxazosin, terazosin, tamsulosin, alfuzosin.

B) Patient has tried a 5α-reductase inhibitor.

Note: Examples of 5α-reductase inhibitor includes finasteride, dutasteride.

Note: For men with erectile dysfunction and benign prostatic hyperplasia, use criterion 1 above.

4. Prophylaxis After Radical Prostatectomy (Early Penile Rehabilitation). Approve for 1 year in patients who meet the following criteria (A and B):

A) Patient had radical prostatectomy within the previous 12 months; AND

B) The medication is prescribed by or in consultation with an urologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of vardenafil (Levitra, generics) or vardenafil orally disintegrating tablets (Staxyn, generics) is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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2. Staxyn™ orally disintegrating tablets [prescribing information]. Research Triagnle Park, NC: GlaxoSmithKline; August 2017.
3. Caglayan E, Huntgeburth M, Karasch T, et al. Phosphodiesterase type 5 inhibition is a novel therapeutic option in Raynaud disease. *Arch Intern Med*. 2006;166:231-233.
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9. Montorsi F, Brock G, Lee J, et al. Effect of nightly versus on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. *Eur Urol.* 2008;54:924-931.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes	08/22/2018
Annual Revision	Generic Levitra and generic Staxyn were added to the policy. No criteria changes.	08/28/2019
Annual Revision	Raynaud's Phenomenon: Moved examples of calcium channel blockers, α-adrenergic blockers, angiotensin converting enzyme inhibitors, and vasodilators to a note. Benign Prostatic Hyperplasia: Moved examples of α_1-blockers and 5α-reductase inhibitors to a note. Removal of the following Condition Not Recommended for Approval: Pulmonary arterial hypertension. Removal of ICD-9 codes from automation. ICD-10 codes still applicable.	09/23/2020

PRIOR AUTHORIZATION POLICY

POLICY: Erythropoiesis-Stimulating Agents – Aranesp Prior Authorization Policy

- Aranesp® (darbepoetin alfa for intravenous or subcutaneous use – Amgen)

REVIEW DATE: 07/22/2020

OVERVIEW

Aranesp, an erythropoiesis-stimulating agent (ESA), is indicated for the following uses:[1]

- **Anemia due to chronic kidney disease** (CKD), including patients on dialysis and patients not on dialysis.
- **Anemia due to chemotherapy in patients with cancer,** in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.

Aranesp has not been shown to improve quality of life, fatigue, or patient well-being.[1] Aranesp is not indicated for use:

- In patients with cancer receiving hormonal agents, biologic products, or radiotherapy unless also receiving concomitant myelosuppressive chemotherapy.
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- In patients with cancer receiving myelosuppressive chemotherapy in whom anemia can be managed by transfusion.
- As a substitute for red blood cell (RBC) transfusions in those who require immediate correction of anemia.

Therapy should be initiated for adult patients with CKD on dialysis when the hemoglobin (Hb) level is < 10.0 g/dL and if the Hb level approaches or exceeds 11.0 g/dL, reduce or interrupt the Aranesp dose.[1] For adult patients with CKD not on dialysis, Aranesp should be initiated when Hb is < 10.0 g/dL and other considerations apply (e.g., patient is likely to need transfusions). If the Hb level exceeds 10.0 g/dL, reduce or interrupt the Aranesp dose and use the lowest dose sufficient to reduce the need for RBC transfusions. Initiate Aranesp for patients on cancer chemotherapy only if the Hb is < 10.0 g/dL. Use the lowest dose of Aranesp to avoid RBC transfusions. For pediatric patients with CKD, initiate Aranesp when the Hb < 10.0 g/dL and if the Hb level approaches 12.0 g/dL, reduce or interrupt the dose of Aranesp.

Guidelines

The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for anemia in CKD (2012) state that for adults with CKD on dialysis, ESA therapy should be used to avoid having the Hb concentration fall below 9.0 g/dL by initiating ESA therapy when the Hb is between 9.0 and 10.0 g/dL.[2] The guidelines recommend against ESA therapy for adult patients with CKD who are not on dialysis when Hb levels are ≥ 10.0 g/dL. For adult patients with CKD who are not on dialysis with Hb levels < 10.0 g/dL, the decision whether to initiate ESA therapy should be individualized based on many factors (e.g., prior response to iron therapy, the risk of needing a transfusion, presence of symptoms). In general, ESAs should not be used to maintain Hb concentrations above 11.5 g/dL in adult patients with CKD. For pediatric patients with CKD, the Hb concentration in which ESAs should be initiated in the individual patient should be considered while being aware of the potential benefits and potential harms. In all pediatric patients with CKD receiving ESA therapy the selected Hb concentration should be in the range of 11.0 to 12.0 g/dL. Iron supplementation can improve response to ESA therapy. Baseline and periodic monitoring (e.g., iron, total iron-binding capacity, transferrin saturation, or ferritin levels) and instituting iron replacement when needed may be useful in limiting the need for ESAs, maximizing symptomatic improvement in patients, and determining the reason for failure to adequately respond to ESAs. Iron deficiency can occur following continued ESA use and, therefore, iron supplementation is required in most patients to maintain an optimal response.

Clinical practice guidelines from the National Comprehensive Cancer Network (NCCN) for myelodysplastic syndrome (MDS) [version 2.2020 – February 28, 2020] list Aranesp as having utility in anemic, symptomatic patients with MDS if serum erythropoietin levels are ≤ 500 mU/mL.[3] Iron stores should be adequate. Due to safety issues, the guidelines suggest that ESAs be used in the management of symptomatic anemia in patients with MDS and to aim for a target Hb ≤ 12.0 g/dL. The NCCN guidelines for myeloproliferative neoplasms (version 1.2020 – May 21, 2020) address Aranesp and epoetin alfa products as options for treatment of patients with anemia related to myelofibrosis having a serum erythropoietin level ≤ 500 mU/mL.[4] Iron stores should be adequate. The guidelines also advise that ESAs are not effective for the management of transfusion-dependent anemia.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Aranesp in patients with conditions other than CKD who are on dialysis. The intent of this policy is to provide recommendations for uses other than anemia in patients with CKD who are on dialysis. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Aranesp as well as the monitoring required for adverse events and long-term efficacy, approval requires Aranesp to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Aranesp is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Anemia in Patients with Chronic Kidney Disease who are on Dialysis.** Approve for 3 years.

2. **Anemia in Patients with Chronic Kidney Disease who are not on Dialysis.** Approve for 1 year if the patient meets the following criteria (A or B):
   - **A)** Initial Therapy. Approve if the patient meets the following criteria (i and ii):
     - **i.** Patient meets one of the following (a or b):
       - **a)** Patient is ≥ 18 years of age with a hemoglobin < 10.0 g/dL; OR
       - **b)** Patient is < 18 years of age with a hemoglobin ≤ 11.0 g/dL; AND
     - **ii.** Patient meets one of the following (a or b):
       - **a)** Patient is currently receiving iron therapy; OR
       - **b)** Patient has adequate iron stores according to the prescriber; OR
   - **B)** Patient is currently receiving an erythropoiesis-stimulating agent (ESA). Approve if the patient meets the following criteria (i and ii):

     Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit), a darbepoetin alfa product (e.g., Aranesp), or a methoxy polyethylene glycol-epoetin beta product (e.g., Mircera).
     - **i.** Patient meets one of the following (a or b):
       - **a)** Patient is ≥ 18 years of age with a hemoglobin < 11.5 g/dL; OR
       - **b)** Patient is < 18 years of age with a hemoglobin ≤ 12.0 g/dL; AND
     - **ii.** Patient meets one of the following (a or b):
       - **a)** Patient is currently receiving iron therapy; OR
       - **b)** Patient has adequate iron stores according to the prescriber.

3. **Anemia in Patients with Cancer due to Cancer Chemotherapy.** Approve for 6 months if the patient meets the following criteria (A or B):
   - **A)** Initial Therapy. Approve if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient has a hemoglobin < 10.0 g/dL; AND
     - **ii.** Patient is currently receiving myelosuppressive chemotherapy; AND
     - **iii.** Patient meets one of the following (a or b):
       - **a)** Patient is currently receiving iron therapy; OR
       - **b)** Patient has adequate iron stores according to the prescriber; OR
   - **B)** Patient is currently receiving an erythropoiesis-stimulating agent (ESA). Approve if the patient meets the following criteria (i, ii, and iii):

     Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit), or a darbepoetin alfa product (e.g., Aranesp).
     - **i.** Patient has a hemoglobin ≤ 12.0 g/dL; AND
     - **ii.** Patient is currently receiving myelosuppressive chemotherapy; AND
     - **iii.** Patient meets one of the following (a or b):
       - **a)** Patient is currently receiving iron therapy; OR
       - **b)** Patient has adequate iron stores according to the prescriber.

Other Uses with Supportive Evidence

4. **Anemia Associated with Myelodysplastic Syndrome (MDS).** Approve for 1 year if the patient meets the following criteria (A or B):
   - **A)** Initial Therapy. Approve if the patient meets the following criteria (i, ii, iii, and iv):
     - **i.** Patient meets one of the following (a or b):
       - **a)** Patient has a hemoglobin < 10.0 g/dL; OR

b) Patient has a serum erythropoietin level ≤ 500 mU/mL; AND

ii. Patient is ≥ 18 years of age; AND

iii. Aranesp is prescribed by or in consultation with a hematologist or oncologist; AND

iv. Patient meets one of the following (a or b):

a) Patient is currently receiving iron therapy; OR

b) Patient has adequate iron stores according to the prescriber; OR

B) Patient is currently receiving an erythropoiesis-stimulating agent (ESA). Approve if the patient meets the following criteria (i, ii, iii, and iv):

Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit), or a darbepoetin alfa product (e.g., Aranesp).

i. Patient has a hemoglobin ≤ 12.0 g/dL; AND

ii. Patient is ≥ 18 years of age; AND

iii. Aranesp is prescribed by or in consultation with a hematologist or oncologist; AND

iv. Patient meets one of the following (a or b):

a) Patient is currently receiving iron therapy; OR

b) Patient has adequate iron stores according to the prescriber.

5. Anemia Associated with Myelofibrosis. Approve for the duration noted below if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following criteria (i, ii, and iii):

i. Patient meets one of the following (a or b):

a) Patient has a hemoglobin < 10.0 g/dL; OR

b) Patient has a serum erythropoietin level ≤ 500 mU/mL; AND

ii. The agent is prescribed by or in consultation with a hematologist or oncologist; AND

iii. Patient meets one of the following (a or b):

a) Patient is currently receiving iron therapy; OR

b) Patient has adequate iron stores according to the prescriber; OR

B) Patient is currently receiving an erythropoiesis-stimulating agent (ESA) therapy. Approve for 1 year if the patient meets the following criteria (i, ii, iii, and iv):

Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit), or a darbepoetin alfa product (e.g., Aranesp).

i. Patient has a hemoglobin ≤ 12.0 g/dL; AND

ii. The ESA therapy is prescribed by or in consultation with a hematologist or oncologist; AND

iii. Patient meets one of the following (a or b):

a) Patient is currently receiving iron therapy; OR

b) Patient has adequate iron stores according to the prescriber; AND

iv. According to the prescriber, patient has responded to therapy defined as hemoglobin ≥ 10 g/dL or a hemoglobin increase of ≥ 2 g/dL.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Aranesp is not recommended in the following situations:

1. Anemia Associated with Cancer in Patients not Receiving Myelosuppressive Cancer Chemotherapy. Aranesp is not indicated in patients with cancer who are not receiving cancer chemotherapy.[1]

2. Anemia Associated with Acute Myelogenous Leukemias (AML), Chronic Myelogenous Leukemias (CML) or other Myeloid Cancers. Aranesp is indicated for use in non-myeloid cancers. AML and CML are examples of myeloid cancers.[1]

3. Anemia Associated with Radiotherapy in Cancer. Aranesp is not indicated for use in patients with cancer who are given only radiation therapy.[1]

4. To Enhance Athletic Performance. Aranesp is not recommended for approval because this indication is excluded from coverage in a typical pharmacy benefit.

5. **Anemia due to Acute Blood Loss.** Use of Aranesp is not appropriate in these types of situations.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Aranesp® injection for intravenous or subcutaneous use [prescribing information]. Thousand Oaks, CA: Amgen, Inc.; January 2019.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int*. 2012;2(Suppl):279-335.
3. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (version 2.2020 – February 28, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 29, 2020.
4. The NCCN Myeloproliferative Neoplasms Clinical Practice Guidelines in Oncology (version 1.2020 – May 21, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 29, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	Criteria that previously stated Epogen/Procrit were changed to cite epoetin alfa to address the approval of Retacrit. For patients with anemia due to CKD who are on dialysis, the criteria were changed to reflect approval of Mircera in pediatric patients who are on hemodialysis. For patients requesting to use Aranesp who are currently receiving Mircera, the target Hb of ≤ 12.0 g/dL was added for children, similar to other ESA. Previously, the criteria only addressed the Hb threshold in adults (≤ 11.5 g/dL) who were receiving Mircera and requesting to transition to Aranesp.	06/20/2018
Annual revision	The following changes were made: 1. **Anemia in CKD for Patients Who are on Dialysis:** The approval duration was changed from 6 months to 1 year. For the criteria that requires the patient have a specified Hb value, changed the wording of "adults" to "patients ≥ 18 years of age". For the criteria that requires children to have a specified Hb value, changed the wording of "children" to "patients < 18 years of age". For the criteria that addresses patients who are currently receiving an ESA, changed from citing examples of the ESA products in criteria to providing a list of ESAs in a note. The example cited that the "Aranesp prescribing information recommends supplemental iron therapy when serum ferritin is < 100 mcg/L or when serum transferrin saturation is < 20%" was deleted. 2. **Anemia in CKD for Patients Who are Not on Dialysis:** The approval duration was changed from 6 months to 1 year. For the criteria that requires the patient have a specified Hb value, changed the wording of "adults" to "patients ≥ 18 years of age". For the criteria that requires children to have a specified Hb value, changed the wording of "children" to "patients < 18 years of age". For the criteria that addresses patients who are currently receiving an ESAs, changed from citing examples of the ESA products in criteria to providing a list of ESAs in a note. The example cited that the "Aranesp prescribing information recommends supplemental iron therapy when serum ferritin is < 100 mcg/L or when serum transferrin saturation is < 20%" was deleted. 3. **Anemia in Patients with Cancer Due to Cancer Chemotherapy:** The approval duration was changed from 4 months to 6 months. For the criteria that addresses patients who are currently receiving an ESA, changed from citing examples of the ESA products in criteria to providing a list of ESAs in a note. The example cited that the "Aranesp prescribing information recommends supplemental iron therapy when serum ferritin is < 100 mcg/L or when serum transferrin saturation is < 20%" was deleted. 4. **Anemia Associated with MDS:** The approval duration was changed from 6 months to 1 year. For the criteria that addresses patients who are currently receiving an ESAs, changed from citing examples of the ESA products in criteria to providing a list of ESAs in a note. Initial approval and extended approval as a separate section was removed, including the criteria that defined response. The example cited that the "Aranesp prescribing information recommends supplemental iron therapy when serum ferritin is < 100 mcg/L or when serum transferrin saturation is < 20%" was deleted. 5. **Anemia Associated with Myelofibrosis:** New criteria were approved.	07/24/2019

Selected revision	**Anemia in CKD for Patients Who are on Dialysis.** Existing criteria were removed. This indication is no longer a targeted indication for this policy. All requests for anemia in CKD for patients who are on dialysis changed to approve for 1 year.	9/11/2019
Selected revision	For **Anemia in Patients with Chronic Kidney Disease who are on Dialysis,** the approval duration was changed from 1 year to 3 years.	11/06/2019
Annual Revision	No criteria changes.	07/22/2020

PRIOR AUTHORIZATION POLICY

POLICY: Erythropoiesis-Stimulating Agents – Epoetin Alfa Products Prior Authorization Policy

- Epogen® (epoetin alfa injection for intravenous or subcutaneous use – Amgen)
- Procrit® (epoetin alfa injection for intravenous or subcutaneous use – Janssen)
- Retacrit™ (epoetin alfa-epbx injection for intravenous and subcutaneous use Pfizer/Hospira)

REVIEW DATE: 07/22/2020

OVERVIEW

Epoetin alfa (Epogen, Procrit, Retacrit), an erythropoiesis-stimulating agent (ESA), is indicated for the following uses:[1-3]

- **Anemia due to chronic kidney disease** (CKD), including patients on dialysis and patients not on dialysis to decrease the need for red blood cell (RBC) transfusions.
- **Anemia due to chemotherapy in patients with cancer**, in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.
- **Anemia due to zidovudine**, in patients with human immunodeficiency virus (HIV) infection.
- **Reduction of allogeneic RBC transfusions**, in patients with perioperative hemoglobin (Hb) > 10.0 to ≤ 13.0 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery.

Epoetin alfa has not been shown to improve quality of life, fatigue, or patient well-being.[1-3] Epoetin alfa is not indicated for use:

- In patients with cancer receiving hormonal agents, biologic products, or radiotherapy unless also receiving concomitant myelosuppressive chemotherapy.
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- In patients with cancer receiving myelosuppressive chemotherapy in whom anemia can be managed by transfusion.
- In patients scheduled for surgery who are willing to donate autologous blood.
- In patients undergoing cardiac or vascular surgery.
- As a substitute for RBC transfusions in those who require immediate correction of anemia.

Therapy should be initiated for patients with CKD on dialysis when the Hb level is < 10.0 g/dL and if the Hb level approaches or exceeds 11.0 g/dL, reduce or interrupt the dose of epoetin alfa.[1-3] For adults with CKD who are not on dialysis, epoetin alfa should be initiated when the Hb is < 10.0 g/dL and other considerations apply (e.g., patient is likely to need transfusions). If the Hb exceeds 10.0 g/dL, reduce or interrupt the epoetin alfa dose and use the lowest dose sufficient to reduce the need for RBC transfusions. Epoetin alfa is indicated for the treatment of anemia due to zidovudine given at ≤ 4,200 mg per week in HIV-infected patients with endogenous serum erythropoietin levels of ≤ 500 mU/mL. It is recommended to withhold epoetin alfa if Hb exceeds 12.0 g/dL. Data show that epoetin alfa elevated or maintained Hb and/or hematocrit and decreased transfusions in anemic patients (Hb < 10.0 g/dL) who were receiving zidovudine. Patients with baseline endogenous serum erythropoietin levels ≤ 500 mU/mL derived greater benefit with epoetin alfa (e.g., achievement of higher hematocrit, reduction in transfusion requirements) compared

with those having levels greater than this threshold. Initiate epoetin alfa for patients on cancer chemotherapy only if the Hb is < 10.0 g/dL. Use the lowest dose of epoetin alfa necessary to avoid RBC transfusions. Hb can be increased to (or near) a concentration of 12.0 g/dL at which time the dose of epoetin alfa should be titrated to maintain that level.

Guidelines

The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for anemia in CKD (2012) state that for adults with CKD on dialysis ESA therapy should be used to avoid having the Hb concentration fall below 9.0 g/dL by initiating ESA therapy when the Hb is between 9.0 and 10.0 g/dL.[4] The guidelines recommend against ESA therapy for adult patients with CKD who are not on dialysis when Hb levels are ≥ 10.0 g/dL. For adult patients with CKD who are not on dialysis with Hb levels < 10.0 g/dL, the decision whether to initiate ESA therapy should be individualized based on many factors (e.g., prior response to iron therapy, the risk of needing a transfusion, presence of symptoms). In general, ESAs should not be used to maintain Hb concentrations above 11.5 g/dL in adult patients with CKD. For pediatric patients with CKD, the Hb concentration in which ESAs should be initiated in the individual patient should be considered while being aware of the potential benefits and potential harms. In all pediatric patients with CKD receiving ESA therapy, the selected Hb concentration should be in the range of 11.0 to 12.0 g/dL. Iron supplementation can improve response to ESA therapy. Baseline and periodic monitoring (e.g., iron, total iron-binding capacity, transferrin saturation, or ferritin levels) and instituting iron replacement when needed may be useful in limiting the need for ESAs, maximizing symptomatic improvement in patients, and determining the reason for failure to adequately respond to ESAs. Iron deficiency can occur following continued ESA use and, therefore, iron supplementation is required in most patients to maintain an optimal response.

Clinical practice guidelines from the National Comprehensive Cancer Network (NCCN) for myelodysplastic syndrome (MDS) [version 2.2020 – February 28, 2020] list Epoetin alfa as having utility in anemic, symptomatic patients with MDS if serum erythropoietin levels are ≤ 500 mU/mL.[5] Iron stores should be adequate. Due to safety issues, the guidelines suggest that ESAs be used in the management of symptomatic anemia in patients with MDS and to aim for a target Hb ≤ 12.0 g/dL. The NCCN guidelines for myeloproliferative neoplasms (version 1.2020 – May 21, 2020) address Aranesp and epoetin alfa products as options for treatment of patients with anemia related to myelofibrosis having a serum erythropoietin level ≤ 500 mU/mL.[6] Iron stores should be adequate. The guidelines also advise that ESAs are not effective for the management of transfusion-dependent anemia.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of epoetin alfa products in patients with conditions other than CKD who are on dialysis. The intent of this policy is to provide recommendations for uses other than anemia in patients with CKD who are on dialysis. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with epoetin alfa as well as the monitoring required for adverse events and long-term efficacy, approval requires epoetin alfa to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of epoetin alfa is recommended in those who meet the following criteria:

FDA-Approved Indications

4. **Anemia in Patients with Chronic Kidney Disease who are on Dialysis.** Approve for 3 years.

5. **Anemia in Patients with Chronic Kidney Disease who are not on Dialysis.** Approve for 1 year if the patient meets the following criteria (A or B):
   - **C)** Initial Therapy. Approve if the patient meets the following criteria (i and ii):
     - **iii.** Patient meets one of the following (a or b):
       - **c)** Patient is ≥ 18 years of age with a hemoglobin < 10.0 g/dL; OR

d) Patient is < 18 years of age with a hemoglobin ≤ 11.0 g/dL; AND

iv. Patient meets one of the following (a or b):

c) Patient is currently receiving iron therapy; OR

d) Patient has adequate iron stores according to the prescriber; OR

D) Patient is currently receiving an erythropoiesis-stimulating agent (ESA). Approve if the patient meets the following criteria (i and ii):

Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit), a darbepoetin alfa product (e.g., Aranesp), or a methoxy polyethylene glycol-epoetin beta product (e.g., Mircera).

iii. Patient meets one of the following (a or b):

c) Patient is ≥ 18 years of age with a hemoglobin < 11.5 g/dL; OR

d) Patient is < 18 years of age with a hemoglobin ≤ 12.0 g/dL; AND

iv. Patient meets one of the following (a or b):

c) Patient is currently receiving iron therapy; OR

d) Patient has adequate iron stores according to the prescriber.

6. Anemia in Patients with Cancer due to Cancer Chemotherapy. Approve for 6 months if the patient meets the following criteria (A or B):

C) Initial Therapy. Approve if the patient meets the following criteria (i, ii, and iii):

iv. Patient has a hemoglobin < 10.0 g/dL; AND

v. Patient is currently receiving myelosuppressive chemotherapy; AND

vi. Patient meets one of the following (a or b):

c) Patient is currently receiving iron therapy; OR

d) Patient has adequate iron stores according to the prescriber; OR

D) Patient is currently receiving an erythropoiesis-stimulating agent (ESA). Approve if the patient meets the following criteria (i, ii, and iii):

Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit), or a darbepoetin alfa product (e.g., Aranesp).

iv. Patient has a hemoglobin ≤ 12.0 g/dL; AND

v. Patient is currently receiving myelosuppressive chemotherapy; AND

vi. Patient meets one of the following (a or b):

c) Patient is currently receiving iron therapy; OR

d) Patient has adequate iron stores according to the prescriber.

4. Patients with Anemia and Human Immunodeficiency Virus who are Receiving Zidovudine. Approve for 1 year if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve if the patient meets the following criteria (i, ii, and iii):

i. Patient meets one of the following (a or b):

a) Patient has a hemoglobin < 10.0 g/dL; OR

b) Patient has a serum erythropoietin level is ≤ 500 mU/mL; AND

ii. Patient is currently receiving zidovudine therapy; AND

iii. Patient meets one of the following (a or b):

a) Patient is currently receiving iron therapy; OR

b) Patient has adequate iron stores according to the prescriber; OR

B) Patient is currently receiving an erythropoiesis-stimulating agent (ESA). Approve if the patient meets the following criteria (i, ii, and iii):

Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit), or darbepoetin alfa product (e.g., Aranesp).

v. Patient has a hemoglobin ≤ 12.0 g/dL; AND

vi. Patient is currently receiving zidovudine therapy; AND

vii. Patient meets one of the following (a or b):

a) Patient is currently receiving iron therapy; OR

b) Patient has adequate iron stores according to the prescriber.

5. **Reduction of Allogeneic Red Blood Cell Transfusions in Patients Undergoing Surgery.** Approve for 1 month if the patient meets the following criteria (A, B, C and D):
   - **A)** Hemoglobin is ≤ 13.0 g/dL; AND
   - **B)** The surgery is elective, nonvascular and noncardiac; AND
   - **C)** Patient is not willing or able to donate autologous blood prior to surgery; AND
   - **D)** Patient meets one of the following (i or ii):
     - **i.** Patient is currently receiving iron therapy; OR
     - **ii.** Patient has adequate iron stores according to the prescriber.

Other Uses with Supportive Evidence

6. **Anemia Associated with Myelodysplastic Syndrome (MDS).** Approve for 1 year if the patient meets the following criteria (A or B):
   - **C)** Initial Therapy. Approve if the patient meets the following criteria (i, ii, iii, and iv):
     - **v.** Patient meets one of the following (a or b):
       - **a)** Patient has a hemoglobin < 10.0 g/dL; OR
       - **b)** Patient has a serum erythropoietin level ≤ 500 mU/mL; AND
     - **vi.** Patient is ≥ 18 years of age; AND
     - **vii.** The agent is prescribed by or in consultation with a hematologist or oncologist; AND
     - **viii.** Patient meets one of the following (a or b):
       - **c)** Patient is currently receiving iron therapy; OR
       - **d)** Patient has adequate iron stores according to the prescriber; OR
   - **B)** Patient is currently receiving an erythropoiesis-stimulating agent (ESA). Approve if the patient meets the following criteria (i, ii, iii, and iv):
     Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit), or a darbepoetin alfa product (e.g., Aranesp).
     - **viii.** Patient has a hemoglobin ≤ 12.0 g/dL; AND
     - **ix.** Patient is ≥ 18 years of age; AND
     - **x.** The agent is prescribed by or in consultation with a hematologist or oncologist; AND
     - **xi.** Patient meets one of the following (a or b):
       - **c)** Patient is currently receiving iron therapy; OR
       - **d)** Patient has adequate iron stores according to the prescriber.

7. **Anemia Associated with Myelofibrosis.** Approve for the duration noted below if the patient meets the following criteria (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient meets one of the following (a or b):
       - **a)** Patient has a hemoglobin < 10.0 g/dL; OR
       - **b)** Patient has a serum erythropoietin level ≤ 500 mU/mL; AND
     - **ii.** The agent is prescribed by or in consultation with a hematologist or oncologist; AND
     - **iii.** Patient meets one of the following (a or b):
       - **a)** Patient is currently receiving iron therapy; OR
       - **b)** Patient has adequate iron stores according to the prescriber; OR
   - **B)** Patient is currently receiving an erythropoiesis-stimulating agent (ESA) therapy. Approve for 1 year if the patient meets the following criteria (i, ii, iii, and iv):
     Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit), or a darbepoetin alfa product (e.g., Aranesp).
     - **i.** Patient has a hemoglobin ≤ 12.0 g/dL; AND
     - **ii.** The ESA therapy is prescribed by or in consultation with a hematologist or oncologist; AND
     - **iii.** Patient meets one of the following (a or b):
       - **a)** Patient is currently receiving iron therapy; OR
       - **b)** Patient has adequate iron stores according to the prescriber; AND
     - **iv.** According to the prescriber, patient has responded to therapy defined as hemoglobin ≥ 10 g/dL or a hemoglobin increase of ≥ 2 g/dL.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Epoetin alfa is not recommended in the following situations:

7. **Anemia Associated with Cancer in Patients not Receiving Myelosuppressive Cancer Chemotherapy.** Epoetin alfa is not indicated in patients with cancer who are not receiving cancer chemotherapy.[1-3]

8. **Anemia Associated with Acute Myelogenous Leukemias (AML), Chronic Myelogenous Leukemias (CML) or other Myeloid Cancers.** Epoetin alfa is indicated for use in non-myeloid cancers. AML and CML are examples of myeloid cancers.[1-3]

9. **Anemia Associated with Radiotherapy in Cancer.** Epoetin alfa is not indicated for use in patients with cancer who are given only radiation therapy.[1-3]

10. **To Enhance Athletic Performance.** Epoetin alfa is not recommended for approval because this indication is excluded from coverage in a typical pharmacy benefit.

11. **Anemia due to Acute Blood Loss.** Use of Epoetin alfa is not appropriate in these types of situations.

12. **Non-Anemic Patients (Hemoglobin [Hb] > 13.0 g/dL) Prior to Surgery.** Although studies have been done that involved non-anemic patients undergoing various surgeries receiving epoetin alfa preoperatively and sometimes postoperatively to prevent transfusions or subsequent anemia, the overall benefit of this therapy in those with relatively normal preoperative Hb level is questionable.

13. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

5. Procrit® injection for intravenous or subcutaneous use [prescribing information]. Horsham, PA: Janssen; May 2020.
6. Epogen® injection for intravenous or subcutaneous use [prescribing information]. Thousand Oaks, CA: Amgen, Inc.; July 2018.
7. Retacrit™ injection for subcutaneous or intravenous use [prescribing information]. New York, NY and Lake Forest, IL: Pfizer and Hospira; June 2020.
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10. The NCCN Myeloproliferative Neoplasms Clinical Practice Guidelines in Oncology (version 1.2020 – May 21, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 29, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	Added Retacrit to the policies with the same approval criteria to that of Epogen and Procrit. The name of the policy was changed from Epogen/Procrit to Epoetin Alfa Products. Criteria that previously stated Epogen/Procrit were changed to state epoetin alfa. Criteria were revised to reflect FDA-approval of Mircera for use in the treatment of anemia associated with chronic kidney disease in pediatric patients who are on hemodialysis. For patients requesting to use epoetin alfa who are currently receiving Mircera, the target Hb of ≤ 12.0 g/dL was added for children, similar to the other ESAs. Previous, the criteria only addressed the hemoglobin threshold in adults (≤ 11.5 g/dL) who were receiving Mircera and requesting to transition to epoetin alfa.	06/20/2018
Annual revision	The following changes were made: 1. **Anemia in CKD for Patients Who are on Dialysis:** The approval duration was changed from 6 months to 1 year. For the criteria that requires the patient have a specified Hb value, changed the wording of "adults" to "patients ≥ 18 years of age". For the criteria that requires children to have a specified Hb value, changed the wording of "children" to "patients < 18 years of age". For the criteria that addresses patients who are currently receiving an ESA, changed from citing examples of the ESA products in criteria to providing a list of ESAs in a note. The example cited that the "Epoetin alfa prescribing information recommends supplemental iron therapy when serum ferritin is < 100 mcg/L or when serum transferrin saturation is < 20%" was deleted. 2. **Anemia in CKD for Patients Who are Not on Dialysis:** The approval duration was changed from 6 months to 1 year. For the criteria that requires the patient have a specified Hb value, changed the wording of "adults" to "patients ≥ 18 years of age". For the criteria that requires children to have a specified Hb value, changed the wording of "children" to "patients < 18 years of age". For the criteria that addresses patients who are currently receiving an ESA, changed from citing examples of the ESA products in criteria to providing a list of ESAs in a note. The example cited that the "Epoetin alfa prescribing information recommends supplemental iron therapy when serum ferritin is < 100 mcg/L or when serum transferrin saturation is < 20%" was deleted. 3. **Patients with Anemia and HIV who are Receiving Zidovudine:** The duration of therapy was changed from 4 months to 1 year. For the criteria that addresses patients who are currently receiving an ESA, changed from citing examples of the ESA products in criteria to providing a list of ESAs in a note. The example cited that the "Epoetin alfa prescribing information recommends supplemental iron therapy when serum ferritin is < 100 mcg/L or when serum transferrin saturation is < 20%" was deleted. 4. **Anemia in Patients with Cancer Due to Cancer Chemotherapy:** The approval duration was changed from 4 months to 6 months. For the criteria that addresses patients who are currently receiving an ESA, changed from citing examples of the ESA products in criteria to providing a list of ESAs in a note. The example cited that the "Epoetin alfa prescribing information recommends supplemental iron therapy when serum ferritin is < 100 mcg/L or when serum transferrin saturation is < 20%" was deleted. 5. **Reduction of Allogeneic Red Blood Cell Transfusions in Patients Undergoing Surgery:** The example cited that the "Epoetin alfa prescribing information recommends supplemental iron therapy when serum ferritin is < 100 mcg/L or when serum transferrin saturation is < 20%" was deleted. 6. **Anemia Associated with MDS:** The approval duration was changed from 6 months to 1 year. For the criteria that addresses patients who are currently receiving an ESA, changed from citing examples of the ESA products in criteria to providing a list of ESAs in a note. 7. **Anemia Associated with Myelofibrosis:** New criteria were approved. See policy.	07/24/2019
Selected revision	**Anemia in CKD for Patients Who are on Dialysis.** Existing criteria were removed. This indication is no longer a targeted indication for this policy. All requests for anemia in CKD for patients who are on dialysis changed to approve for 1 year.	9/11/2019
Selected revision	For **Anemia in Patients with Chronic Kidney Disease who are on Dialysis,** the approval duration was changed from 1 year to 3 years.	11/06/2019
Annual Revision	No criteria changes.	07/22/2020

PRIOR AUTHORIZATION POLICY

POLICY: Erythropoiesis-Stimulating Agents – Mircera Prior Authorization Policy

- Mircera® (methoxy polyethylene glycol-epoetin beta injection for intravenous or subcutaneous use – Vifor Pharma)

REVIEW DATE: 07/22/2020

OVERVIEW

Mircera, an erythropoiesis-stimulating agent (ESA), is indicated for the following uses:[1]

- **Anemia due to chronic kidney disease** (CKD), including adult patients on dialysis, adult patients not on dialysis, and pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA.

Mircera has not been shown to improve symptoms, physical functioning, or health-related quality of life.[1] Mircera is not indicated for use:

- In the treatment of anemia due to cancer chemotherapy.
- As a substitute for red blood cell (RBC) transfusions in those who require immediate correction of anemia.

Therapy should be initiated for patients with CKD on dialysis when the Hb level is < 10.0 g/dL and if the Hb level approaches or exceeds 11.0 g/dL, reduce or interrupt the dose of Mircera.[1] Patients with CKD not on dialysis, Mircera should be initiated when the Hb is < 10.0 g/dL and other considerations apply (e.g., patient is likely to need transfusions). If the Hb exceeds 10.0 g/dL, reduce or interrupt the Mircera dose and use the lowest dose sufficient to reduce the need for RBC transfusions.

Guidelines

The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for anemia in CKD (2012) state that for adults with CKD on dialysis ESA therapy should be used to avoid having the Hb concentration fall below 9.0 g/dL by initiating ESA therapy when the Hb is between 9.0 and 10.0 g/dL.[2] The guidelines recommend against ESA therapy for adult patients with CKD who are not on dialysis when Hb levels are ≥ 10.0 g/dL. For adult patients with CKD who are not on dialysis with Hb levels < 10.0 g/dL, the decision whether to initiate ESA therapy should be individualized based on many factors (e.g., prior response to iron therapy, the risk of needing a transfusion, presence of symptoms). In general, ESAs should not be used to maintain Hb concentrations above 11.5 g/dL in adult patients with CKD. For pediatric patients with CKD, the Hb concentration in which ESAs should be initiated in the individual patient should be considered while being aware of the potential benefits and potential harms. In all pediatric patients with CKD receiving ESA therapy, the selected Hb concentration should be in the range of 11.0 to 12.0 g/dL. Iron supplementation can improve response to ESA therapy. Baseline and periodic monitoring (e.g., iron, total iron-binding capacity, transferrin saturation, or ferritin levels) and instituting iron replacement when needed may be useful in limiting the need for ESAs, maximizing symptomatic improvement in patients, and determining the reason for failure to adequately respond to ESAs. Iron deficiency can occur following continued ESA use and, therefore, iron supplementation is required in most patients to maintain an optimal response.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Mircera in patients with conditions other than CKD who are on dialysis. The intent of this policy is to provide recommendations for uses other than anemia in patients with CKD who are on dialysis. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Mircera as well as the monitoring required for adverse events and long-term efficacy, approval requires Mircera to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mircera is recommended in those who meet the following criteria:

FDA-Approved Indications

7. **Anemia in Patients with Chronic Kidney Disease who are on Dialysis.** Approve for 3 years.

8. **Anemia in Patients with Chronic Kidney Disease who are not on Dialysis.** Approve for 1 year if the patient meets the following criteria (A or B):
   - **A)** Initial Therapy. Approve if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has a hemoglobin < 10.0 g/dL; AND
     - **iii.** Patient meets one of the following (a or b):
       - **a)** Patient is currently receiving iron therapy; OR
       - **b)** Patient has adequate iron stores according to the prescriber; OR
   - **B)** Patient is currently receiving an erythropoiesis-stimulating agent (ESA). Approve if the patient meets the following criteria (i, ii, and iii):

     Note: Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen, Procrit, or Retacrit), a darbepoetin alfa product (e.g., Aranesp), or a methoxy polyethylene glycol-epoetin beta product (e.g., Mircera).
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has a hemoglobin < 11.5 g/dL; AND
     - **iii.** Patient meets one of the following (a or b):
       - **a)** Patient is currently receiving iron therapy; OR
       - **b)** Patient has adequate iron stores according to the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Mircera is not recommended in the following situations:

14. **Anemia Associated with Cancer in Patients Receiving Myelosuppressive Cancer Chemotherapy.** Mircera is not indicated and not recommended for the treatment of anemia due to cancer chemotherapy.[1]

15. **To Enhance Athletic Performance.** Aranesp is not recommended for approval because this indication is excluded from coverage in a typical pharmacy benefit.

16. **Anemia due to Acute Blood Loss.** Use of Aranesp is not appropriate in these types of situations.

17. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	No criteria changes.	02/14/2018
Early annual revision	Criteria that mentioned Epogen/Procrit were changed to epoetin alfa to reflect approval of Retacrit, the first biosimilar epoetin alfa product. For the criteria regarding patients with anemia in CKD who are on dialysis, the criteria that the patient be ≥ 18 years of age was changed to ≥ 5 years of age. For this indication, in patients receiving Mircera for initial therapy for anemia in CKD for patients who are on dialysis, it was noted that the Hb value was required to be ≤ 11.0 g/dL for children initiating therapy; for patients currently receiving Mircera, the Hb value is required to be ≤ 12.0 g/dL in children.	06/20/2018

Annual revision	The following changes were made: 1. **Anemia in CKD for Patients Who are on Dialysis:** The approval duration was changed from 6 months to 1 year. For the criteria that requires the patient have a specified Hb value, changed the wording of "adults" to "patients ≥ 18 years of age". For the criteria that requires children to have a specified Hb value, changed the wording of "children" to "patients < 18 years of age". For the criteria that addresses patients who are currently receiving an ESA, changed from citing examples of the ESA products in criteria to providing a list of ESAs in a note. The example cited that the "Mircera prescribing information recommends supplemental iron therapy when serum ferritin is < 100 mcg/L or when serum transferrin saturation is < 20%" was deleted. 2. **Anemia in CKD for Patients Who are Not on Dialysis:** The approval duration was changed from 6 months to 1 year. For the criteria that requires the patient have a specified Hb value, changed the wording of "adults" to "patients ≥ 18 years of age". For the criteria that requires children to have a specified Hb value, changed the wording of "children" to "patients < 18 years of age". For the criteria that addresses patients who are currently receiving an ESA, changed from citing examples of the ESA products in criteria to providing a list of ESAs in a note. The example cited that the "Mircera prescribing information recommends supplemental iron therapy when serum ferritin is < 100 mcg/L or when serum transferrin saturation is < 20%" was deleted.	07/24/2019
Selected revision	**Anemia in CKD for Patients Who are on Dialysis.** Existing criteria were removed. This indication is no longer a targeted indication for this policy. All requests for anemia in CKD for patients who are on dialysis changed to approve for 1 year.	9/11/2019
Selected revision	For **Anemia in Patients with Chronic Kidney Disease who are on Dialysis,** the approval duration was changed from 1 year to 3 years.	11/06/2019
Annual revision	No criteria changes.	7/22/2020

PRIOR AUTHORIZATION POLICY

POLICY: Fabry Disease – Galafold Prior Authorization Policy

- Galaford® (migalastat capsules – Amicus Therapeutics, Inc.)

REVIEW DATE: 09/30/2020

OVERVIEW

Galafold is indicated for the treatment of adults with a confirmed diagnosis of Fabry disease and an amenable galactosidase alpha gene (GLA) variant based on in vitro assay data.[1] Certain GLA variants produce abnormally folded and less stable forms of the α-galactosidase A (α-GAL) enzyme, however the enzyme still retains activity. Galafold is a pharmacologic chaperone which binds to the active site of α-GAL, which stabilizes the enzyme and allows it to be trafficked from the endoplasmic reticulum to lysosomes. In the lysosome, Galafold dissociates from the enzyme allowing it to exert its pharmacologic activity.

Disease Overview

Fabry disease is a rare inherited X-linked lysosomal storage disorder due to absent or significantly reduced α-Gal activity leading to the accumulation of globotriaosylceramide (GL-3) in a wide variety of cells throughout the body.[2-4] The accumulation of GL-3 leads to progressive multisystem disease, primarily impacting the kidney, heart, and nervous system.[3,4] Life expectancy in patients with Fabry disease is reduced, median survival is typically 50 to 55 years in men and 70 years in women.[2]

The disease can be divided into two phenotypes, a severe, classical phenotype typically found in men without α-Gal activity, and a generally milder non-classical phenotype in men and women with some residual α-Gal activity.[2,3] Classical Fabry disease symptoms often seen at presentation include neuropathic pain, cornea verticillata, and angiokeratoma,[3] and can occur in males as young as 6 to 8 years of age and at 9 years of age in females.[4] Long–term consequences of Fabry disease include hypertrophic

cardiomyopathy, arrhythmias, renal failure, and stroke.[3] Individuals with some residual α-Gal activity typically develop non-classical Fabry disease, which has a later onset, variable disease course, is typically less severe and may affect a single organ, most commonly the heart.[2,3] Despite Fabry disease being an X–linked disorder, women often have Fabry disease signs and symptoms, however they typically have less severe disease than men.

Currently, there have been more than 800 mutations to the gene encoding α-Gal identified and about 60% are missense mutations resulting in single amino acid substitutions.[5] Some of these mutated enzymes have activity levels similar to normal α-Gal however they have been found to be unstable and are retained in the endoplasmic reticulum.

Guidelines

Current Fabry disease treatment guidelines either do not mention Galafold as a treatment option or discuss it as an investigational agent.[6,7]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Galafold. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Galafold as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Galafold to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Galafold is recommended in those who meet the following criteria:

FDA-Approved Indications

41. Fabry Disease. Approve for 3 years if the patient meets the following criteria (A, B, and C):
- ~~**32.**~~ Patient is ≥ 18 years of age; AND
- ~~**33.**~~ Patient has an amenable galactosidase alpha gene (GLA) variant based on *in vitro* assay data; AND
- **34.** The medication is prescribed by or in consultation with a geneticist, nephrologist, or a physician who specializes in the treatment of Fabry disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Galafold is not recommended in the following situations:

105. Concurrent Use with Fabrazyme. One small study (n = 23) assessed a single dose of Galafold (150 mg or 450 mg) used concurrently with Fabrazyme or agalsidase alpha. While a single dose of Galafold significantly increased α-GAL activity, the long-term safety and efficacy of concurrent use of Galafold and Fabrazyme has not been established.[8] Galafold is not FDA approved for concurrent use with Fabrazyme.

106. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/13/2018
Annual Review	No change to the criteria	10/02/2019
Annual Revision	No criteria changes.	09/30/2020

PRIOR AUTHORIZATION POLICY

POLICY: Gamifant Prior Authorization Policy

- Gamifant® (emapalumab-lzsg for intravenous injection – Sobi)

REVIEW DATE: 12/02/2020

OVERVIEW

Gamifant, an anti-interferon gamma (IFN-γ) antibody, is indicated for the treatment of adult and pediatric patients with **primary hemophagocytic lymphohistiocytosis** (HLH) with refractory, recurrent, or progressive disease or intolerance with conventional HLH therapy.[1]

Disease Overview

HLH is a syndrome characterized by signs and symptoms of extreme inflammation, caused by defects in cytotoxic function (cytotoxic T cells and natural killer cells).[2] The incidence is estimated at 1.2 cases per million individuals per year, but this is likely an underestimate.[3] In healthy individuals, cytotoxic function is important to terminate immune responses when appropriate by targeting and destroying activated immune cells. Deficiencies in cytotoxic function lead to an unchecked immune response and hyper-inflammation. Primary HLH has a clear genetic cause, whereas secondary HLH is triggered by a concomitant infection or medical condition, such as Epstein-Barr virus infection, malignancy, or rheumatologic disorders. IFN-γ normally has both pro-inflammatory functions (e.g., macrophage activation) and anti-inflammatory functions (e.g., activation of cytotoxic cells).[4,5] However, in HLH, the anti-inflammatory action of IFN-γ is ineffective due to impaired cytotoxic cell activity; thus, pro-inflammatory effects predominate.

Guidelines

The HLH-2004 treatment protocol, developed by the Histiocyte Society, is the current standard of care for diagnostic and therapeutic guidelines.[6] Gamifant is not addressed in the 2004 protocol. To establish a diagnosis of HLH, patients must either have a molecular diagnosis consistent with HLH or meet five out of eight diagnostic criteria. A backbone of etoposide and systemic dexamethasone is the conventional standard of care to induce symptomatic resolution; cyclosporine A and anti-thymocyte globulin have also demonstrated efficacy. Although chemotherapy prolongs survival in primary HLH, a hematopoietic stem cell transplant (HSCT) is needed for cure. Patients with primary HLH should continue chemotherapy (usually with etoposide, cyclosporine A, and dexamethasone) until HSCT can be performed. Myelotoxicity due to chemotherapy is a concern, especially since patients with HLH can have severe cytopenias and immunodeficiency at baseline.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Gamifant. Because of the specialized skills required for evaluation and diagnosis of patients treated with Gamifant, approval requires it to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Gamifant is recommended for those who meet the following criteria:

FDA-Approved Indications

5. Hemophagocytic Lymphohistiocytosis, Primary. Approve Gamifant for 6 months in patients meeting all of the following criteria (A, B, C, and D):

- **A)** Patient has a diagnosis of hemophagocytic lymphohistiocytosis determined by at least one of the following (i or ii):
  - **i.** Patient has a molecular genetic diagnosis consistent with hemophagocytic lymphohistiocytosis; OR
  - **ii.** Prior to treatment, the patient meets at least FIVE of the following diagnostic criteria at baseline (FIVE of a, b, c, d, e, f, g, or h):
    - **a)** Fever ≥ 38.5 °C;
    - **b)** Splenomegaly;
    - **c)** Cytopenias defined as at least TWO of the following (1, 2, or 3):
      - **1)** Hemoglobin < 9 g/dL (or < 10 g/dL in infants less than 4 weeks of age);
      - **2)** Platelets < 100 x 10^9/L;
      - **3)** Neutrophils < 1.0 x 10^9/L;
    - **d)** Patient meets one of the following (1 or 2):
      - **1)** Fasting triglycerides ≥ 265 mg/dL; OR
      - **2)** Fibrinogen ≤ 1.5 g/L;
    - **e)** Hemophagocytosis in bone marrow, spleen, or lymph nodes;
    - **f)** Low or absent natural killer cell activity (according to local laboratory reference);
    - **g)** Ferritin ≥ 500 mcg/L;
    - **h)** Soluble CD25 (i.e., soluble interleukin-2 receptor) ≥ 2,400 U/mL; AND
- **B)** Patient has tried at least one conventional therapy (e.g., etoposide, cyclosporine A, or anti-thymocyte globulin); AND
- **C)** According to the prescriber, the patient has experienced at least ONE of the following (i or ii):
  - **i.** Refractory, recurrent, or progressive disease during conventional therapy (e.g., etoposide, cyclosporine A, or anti-thymocyte globulin); OR
  - **ii.** Intolerance to conventional therapy (e.g., etoposide, cyclosporine A, or anti-thymocyte globulin); AND
- **D)** The medication is prescribed by, or in consultation with, a hematologist, oncologist, immunologist, transplant specialist, or physician who specializes in hemophagocytic lymphohistiocytosis or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Gamifant is not recommended in the following situations:

8. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New policy	--	12/19/2018
Annual revision	No criteria changes.	12/18/2019
Annual Revision	No criteria changes.	12/02/2020

PRIOR AUTHORIZATION POLICY

POLICY: Gastroenterology – Gattex Prior Authorization Policy

- Gattex (teduglutide injection for subcutaneous use – NPS Pharmaceuticals)

REVIEW DATE: 06/24/2020

OVERVIEW

Gattex is a glucagon-like peptide-2 (GLP-2) analog indicated for the treatment of short bowel syndrome in patients ≥ 1 year of age who are dependent on parenteral support.[1] In clinical studies, Gattex decreased the volume of parenteral support needed for some patients with short bowel syndrome and intestinal failure. It is administered via a daily subcutaneous injection.

Clinical Efficacy

In a study involving adults (n = 86) with short bowel syndrome requiring parenteral support at least 3 days per week, more patients treated with Gattex through Month 6 achieved ≥ 20% reduction in weekly intravenous volume (63% vs. 30% with placebo).[1] The mean reduction in intravenous volume was 4.4 liters with Gattex vs. 2.3 liters with placebo. When treated over an additional 2 years, the mean reduction from baseline was 7.55 liters. Ten patients were weaned off of nutritional support and remained on Gattex therapy. At Week 24 of a pediatric study, 69% of patients (n = 18/26) reduced parenteral support volume by at least 20% with Gattex. The mean reduction in intravenous volume was -23 mL/kg/day, a 42% reduction in parenteral support. Three patients were weaned off of parenteral nutritional support.

Safety

Gattex has Warnings and Precautions regarding acceleration of neoplastic growth, intestinal obstruction, biliary and pancreatic disease, fluid overload (including congestive heart failure), and increased absorption of concomitant oral medications.[1] It was approved with a Risk Evaluation and Mitigation Strategy (REMS) program intended to inform healthcare providers and patients about serious risks, including the risks of possible acceleration of neoplastic growth and enhancement of colon polyp growth, gastrointestinal (GI) obstruction, and biliary and pancreatic disorders.[2]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Gattex. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Gattex as well as the monitoring required for adverse events and long-term efficacy, approval requires Gattex to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Gattex is recommended in those who meet the following criteria:

FDA-Approved Indications

29. Short Bowel Syndrome. Approve for the duration noted if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

- **i.** Patient is ≥ 1 year of age; AND
- **ii.** Patient meets ONE of the following (a or b):
  - **a)** Patient is currently receiving parenteral nutrition on 3 or more days per week; OR
  - **b)** According to the prescriber, the patient is unable to receive adequate total parenteral nutrition (TPN) required for caloric needs; AND
- **iii.** The medication is prescribed by or in consultation with a gastroenterologist.

B) Patient is Currently Receiving Gattex. Approve for 1 year if the patient meets all of the following (i, ii, and iii):

- **i.** Patient has already received at least 6 months of therapy with Gattex; AND
  Note: A patients who has received < 6 months of continuous therapy should be considered under criterion 1A (Initial Therapy).
- **ii.** According to the prescriber, the patient has experienced at least a 20% decrease from baseline in the weekly volume of parenteral nutrition; AND
- **iii.** The agent is prescribed by or in consultation with a gastroenterologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Gattex is not recommended in the following situations:

45. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	03/13/2019
Early annual revision	**Short Bowel Syndrome:** Due to the updated age indication, change criteria to approve in patients ≥ 1 year of age (previously was ≥ 18 years of age).	06/12/2019
Annual revision	No changes to the criteria.	06/24/2020

PRIOR AUTHORIZATION POLICY

POLICY: Gaucher Disease – Enzyme Replacement Therapy – Cerezyme Prior Authorization Policy

- Cerezyme® (imiglucerase for injection – Genzyme)

REVIEW DATE: 03/17/2021

OVERVIEW

Cerezyme, an analogue of β-glucocerebrosidase, is indicated for the long-term enzyme replacement therapy for pediatric and adult patients with a confirmed diagnosis of **Type 1 Gaucher disease** that results in at least one of the following: anemia, thrombocytopenia, bone disease, hepatomegaly, or splenomegaly.[1]

Cerezyme is produced via recombinant DNA technology in Chinese hamster ovary cells and differs from human placental glucocerebrosidase by one amino acid at position 495.[1] Cerezyme catalyzes the breakdown of glucocerebroside to glucose and ceramide.

Disease Overview

Gaucher disease is a rare autosomal recessive, inherited, lysosomal storage disorder caused by a deficiency of the lysosomal enzyme β-glucocerebrosidase.[2-4] Glucocerebrosidase is responsible for the breakdown of glucosylcerebroside (GluCer) into glucose and ceramide. A deficiency of this enzyme is characterized by an excessive accumulation of GluCer in the visceral organs such as the liver, spleen, and bone marrow. GluCer remains stored within lysosomes causing enlarged lipid-laden macrophages called "Gaucher cells".

Gaucher disease is classified into three phenotypes (Types 1 through 3).[2-5] Type 1 is a non-neuropathic variant with asymptomatic or symptomatic clinical manifestations of splenomegaly, hepatomegaly, anemia, thrombocytopenia, skeletal complications, and occasional lung involvement. Type 2 is an acute neuropathic form characterized by an early onset (3 to 6 months of age) of rapidly progressive neurological disease with visceral manifestations; death generally occurs by the time patients reach 1 to 2 years of age. Type 3 is characterized by neurological symptoms and visceral symptoms with a later onset and includes abnormal eye movements, ataxia, seizures, and dementia. Type 1 is most prevalent in the Western world, accounting for an estimated 94% of patients with Gaucher disease.[2,6] Types 2 and 3 represent < 1% and 5%, respectively, in Europe, North America, and Israel.[2,5] The diagnosis of Gaucher disease is established by demonstrating deficient β-glucocerebrosidase activity in leukocytes or fibroblasts, or mutations in the glucocerebrosidase gene.[7,8]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cerezyme. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cerezyme as well as the monitoring required for adverse events and long-term efficacy, approval requires Cerezyme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cerezyme is recommended in those who meet the following criteria:

FDA-Approved Indications

30. Gaucher Disease. Approve for 1 year if the patient meets the following criteria (A, B, and C):

- **A)** Patient has Type 1 Gaucher disease; AND
- **B)** The diagnosis is established by one of the following (i or ii):
  - **i.** Demonstration of deficient β-glucocerebrosidase activity in leukocytes or fibroblasts; OR
  - **ii.** Molecular genetic testing documenting glucocerebrosidase gene mutation; AND

C) Cerezyme is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cerezyme is not recommended in the following situations:

46. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

109. Cerezyme® for injection [prescribing information]. Cambridge, MA: Genzyme Corporation; December 2020.
110. Burrow TA, Barnes S, and Grabowski GA. Prevalence and management of Gaucher disease. *Pediatric Health Med Ther*. 2011;2:59-73.
111. Cox T. Gaucher disease: clinical profile and therapeutic development. *Biologics*. 2010;4:299-313.
112. Jmoudiak, M. and Futerman, AH. Gaucher disease: Pathological mechanisms and modern management. *Br J Haematol*. 2005;129(2):178–188.
113. Grabowski GA. Lysosomal storage disease 1- phenotype, diagnosis, and treatment of Gaucher's disease. *Lancet*. 2008;372:1263-1271.
114. Zimran A. How I treat Gaucher disease. *Blood*. 2011;118:1463-1471.
115. Stirnemann J, Belmatoug N, Camou F, et al. A review of Gaucher disease pathophysiology, clinical presentation and treatments. *Int J Mol Sci*. 2017;18:441.
116. Baris HN, Cohen IJ, Mistry PK. Gaucher disease: The metabolic defect, pathophysiology, phenotypes and natural history. *Pediatr Endocrinol Rev*. 2014;12:72-81.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	03/20/2019
Annual Revision	No criteria changes	03/25/2020
Annual Revision	**Gaucher Disease:** Moved the designation of "Type 1" disease from the indication to criteria.	03/17/2021

PRIOR AUTHORIZATION POLICY

POLICY: Gaucher Disease – Enzyme Replacement Therapy – Elelyso Prior Authorization Policy

- Elelyso® (taliglucerase for injection – Pfizer)

REVIEW DATE: 03/17/2021

OVERVIEW

Elelyso, an analogue of β-glucocerebrosidase, is indicated for the treatment of patients with a confirmed diagnosis of Type 1 Gaucher disease.[1]

Elelyso is produced via recombinant DNA technology in genetically modified carrot plant root cells.[1] Elelyso differs from human glucocerebrosidase by two amino acids at the N terminal and seven amino acids at the C terminal end of the protein. Elelyso catalyzes the breakdown of glucocerebroside to glucose and ceramide.

Disease Overview

Gaucher disease is a rare autosomal recessive, inherited, lysosomal storage disorder caused by a deficiency of the lysosomal enzyme β-glucocerebrosidase.[2-4] Glucocerebrosidase is responsible for the breakdown of glucosylcerebroside (GluCer) into glucose and ceramide. A deficiency of this enzyme is characterized by an excessive

accumulation of GluCer in the visceral organs such as the liver, spleen, and bone marrow. GluCer remains stored within lysosomes causing enlarged lipid-laden macrophages called "Gaucher cells".

Gaucher disease is classified into three phenotypes (Types 1 through 3).[2-5] Type 1 is a non-neuropathic variant with asymptomatic or symptomatic clinical manifestations of splenomegaly, hepatomegaly, anemia, thrombocytopenia, skeletal complications, and occasional lung involvement. Type 2 is an acute neuropathic form characterized by an early onset (3 to 6 months of age) of rapidly progressive neurological disease with visceral manifestations; death generally occurs by the time patients reach 1 to 2 years of age. Type 3 is characterized by neurological symptoms and visceral symptoms with a later onset and includes abnormal eye movements, ataxia, seizures, and dementia. Type 1 is most prevalent in the Western world, accounting for an estimated 94% of patients with Gaucher disease.[2,6] Types 2 and 3 represent < 1% and 5%, respectively, in Europe, North America, and Israel.[2,5] The diagnosis of Gaucher disease is established by demonstrating deficient β-glucocerebrosidase activity in leukocytes or fibroblasts, or mutations in the glucocerebrosidase gene.[7,8]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Elelyso. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Elelyso as well as the monitoring required for adverse events and long-term efficacy, approval requires Elelyso to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Elelyso is recommended in those who meet the following criteria:

FDA-Approved Indications

31. Gaucher Disease. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient has Type 1 Gaucher disease; AND
- **B)** Patients is ≥ 4 years of age; AND
- **C)** The diagnosis is established by one of the following (i or ii):
  - **i.** Demonstration of deficient β-glucocerebrosidase activity in leukocytes or fibroblasts; OR
  - **ii.** Molecular genetic testing documenting glucocerebrosidase gene mutation; AND
- **D)** Elelyso is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage for Elelyso is not recommended in the following situations:

47. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

117. Elelyso® for injection [prescribing information]. New York, NY: Pfizer; November 2020.
118. Burrow TA, Barnes S, and Grabowski GA. Prevalence and management of Gaucher disease. *Pediatric Health Med Ther*. 2011;2:59-73.
119. Cox T. Gaucher disease: clinical profile and therapeutic development. *Biologics*. 2010;4:299-313.
120. Jmoudiak, M. and Futerman, AH. Gaucher disease: Pathological mechanisms and modern management. *Br J Haematol*. 2005;129(2):178–188.
121. Grabowski GA. Lysosomal storage disease 1- phenotype, diagnosis, and treatment of Gaucher's disease. *Lancet*. 2008;372:1263-1271.
122. Zimran A. How I treat Gaucher disease. *Blood*. 2011;118:1463-1471.

123. Stirnemann J, Belmatoug N, Camou F, et al. A review of Gaucher disease pathophysiology, clinical presentation and treatments. *Int J Mol Sci*. 2017;18:441.
124. Baris HN, Cohen IJ, Mistry PK. Gaucher disease: The metabolic defect, pathophysiology, phenotypes and natural history. *Pediatr Endocrinol Rev*. 2014;12:72-81.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	03/20/2019
Annual Revision	No criteria change	03/25/2020
Annual Revision	**Gaucher Disease:** Moved the designation of "Type 1" disease from the indication to the criteria. A criterion was added that requires the patient to be ≥ 4 years of age.	03/17/2021

PRIOR AUTHORIZATION POLICY

POLICY: Gaucher Disease – Enzyme Replacement Therapy – Vpriv Prior Authorization Policy

- Vpriv® (velaglucerase for injection – Shire Human Genetic Therapies)

REVIEW DATE: 03/17/2021

OVERVIEW

Vpriv, an analogue of β-glucocerebrosidase, is indicated for long-term enzyme replacement therapy for patients with Type 1 Gaucher disease.[1]

Vpriv is produced via gene activation technology in a human fibroblast cell line.[1] Vpriv has the same amino acid sequence as the naturally occurring human glucocerebrosidase. Vpriv catalyzes the breakdown of glucocerebroside to glucose and ceramide.

Disease Overview

Gaucher disease is a rare autosomal recessive, inherited, lysosomal storage disorder caused by a deficiency of the lysosomal enzyme β-glucocerebrosidase.[2-4] Glucocerebrosidase is responsible for the breakdown of glucosylcerebroside (GluCer) into glucose and ceramide. A deficiency of this enzyme is characterized by an excessive accumulation of GluCer in the visceral organs such as the liver, spleen, and bone marrow. GluCer remains stored within lysosomes causing enlarged lipid-laden macrophages called "Gaucher cells".

Gaucher disease is classified into three phenotypes (Types 1 through 3).[2-5] Type 1 is a non-neuropathic variant with asymptomatic or symptomatic clinical manifestations of splenomegaly, hepatomegaly, anemia, thrombocytopenia, skeletal complications, and occasional lung involvement. Type 2 is an acute neuropathic form characterized by an early onset (3 to 6 months of age) of rapidly progressive neurological disease with visceral manifestations; death generally occurs by the time patients reach 1 to 2 years of age. Type 3 is characterized by neurological symptoms and visceral symptoms with a later onset and includes abnormal eye movements, ataxia, seizures, and dementia. Type 1 is most prevalent in the Western world, accounting for an estimated 94% of patients with Gaucher disease.[2,6] Types 2 and 3 represent < 1% and 5%, respectively, in Europe, North America, and Israel.[2,5] The diagnosis of Gaucher disease is established by demonstrating deficient β-glucocerebrosidase activity in leukocytes or fibroblasts, or mutations in the glucocerebrosidase gene.[7,8]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Vpriv. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vpriv as well as the monitoring required for adverse events and long-term efficacy, approval requires Vpriv to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vpriv is recommended in those who meet the following criteria:

FDA-Approved Indications

32. Gaucher Disease. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient has Type 1 Gaucher disease; AND
- **B)** The diagnosis is established by one of the following (i or ii):
  - **i.** Demonstration of deficient β-glucocerebrosidase activity in leukocytes or fibroblasts; OR
  - **ii.** Molecular genetic testing documenting glucocerebrosidase gene mutation; AND
- **C)** Vpriv is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of lysosomal storage disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vpriv is not recommended in the following situations:

48. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

125. Vpriv® for injection [prescribing information]. Lexington, MA: Shire Human Genetic Therapies; December 2020.
126. Burrow TA, Barnes S, and Grabowski GA. Prevalence and management of Gaucher disease. *Pediatric Health Med Ther*. 2011;2:59-73.
127. Cox T. Gaucher disease: clinical profile and therapeutic development. *Biologics*. 2010;4:299-313.
128. Jmoudiak, M. and Futerman, AH. Gaucher disease: Pathological mechanisms and modern management. *Br J Haematol*. 2005;129(2):178–188.
129. Grabowski GA. Lysosomal storage disease 1- phenotype, diagnosis, and treatment of Gaucher's disease. *Lancet*. 2008;372:1263-1271.
130. Zimran A. How I treat Gaucher disease. *Blood*. 2011;118:1463-1471.
131. Stirnemann J, Belmatoug N, Camou F, et al. A review of Gaucher disease pathophysiology, clinical presentation and treatments. *Int J Mol Sci*. 2017;18:441.
132. Baris HN, Cohen IJ, Mistry PK. Gaucher disease: The metabolic defect, pathophysiology, phenotypes and natural history. *Pediatr Endocrinol Rev*. 2014;12:72-81.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	03/20/2019
Annual Revision	No criteria change	03/25/2020
Annual Revision	**Gaucher Disease:** Moved the designation of "Type 1" disease from indication to the criteria.	03/17/2021

PRIOR AUTHORIZATION POLICY

POLICY: Gaucher Disease Substrate Reduction Therapy – Cerdelga® (eliglustat capsules – Genzyme)

DATE REVIEWED: 05/06/2020

OVERVIEW

Cerdelga, a glucosylceramide synthase inhibitor, is indicated for the long-term treatment of adult patients with Gaucher Disease type 1 who are cytochrome P450(CYP)2D6 extensive metabolizers (EMs),

intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test.[1] The Cerdelga prescribing information notes the following limitations of use: patients who are CYP2DE ultra-rapid metabolizers (URMs) may not achieve adequate concentrations of Cerdelga to achieve a therapeutic effect; and a specific dosage cannot be recommended for patients for whom the CYP2D6 genotype cannot be determined (indeterminate metabolizers).

DISEASE OVERVIEW

Gaucher disease is caused by a deficiency in the lysosomal enzyme β-glucocerebrosidase.[1] This enzyme is responsible for the breakdown of glucosylceramide into glucose and ceramide. In Gaucher disease, deficiency of the enzyme β-glucocerebrosidase results in the accumulation of glucosylceramide substrate in lysosomal compartment of macrophages, giving rise to foam cells or "Gaucher cells." Cerdelga is a specific inhibitor of the enzyme glycosylceramide synthase, which is responsible for producing the substrate glucosylceramide; hence Cerdelga functions as a substrate reduction therapy.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Cerdelga. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cerdelga as well as the monitoring required for adverse events and long-term efficacy, approval requires Cerdelga to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cerdelga is recommended in those who meet the following criteria:

FDA-Approved Indications

42. Gaucher Disease Type I. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** The patient is a cytochrome P450(CYP) 2D6 extensive metabolizer (EM), intermediate metabolizer (IM), or poor metabolizer (PM) as detected by an approved test; AND
- **B)** Cerdelga is prescribed by or in consultation with a geneticist, endocrinologist, a metabolic disorder sub-specialist, or a physician who specializes in the treatment of Gaucher Disease or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Cerdelga has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

107. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

29. Cerdelga™ capsules [prescribing information]. Waterford, Ireland: Genzyme; August 2018.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed

New Policy	New criteria	08/23/2017
Early annual revision	No criteria changes	05/09/2018
Annual revision	No changes to the criteria	05/08/2019
Annual revisions	No criteria changes	05/06/2020

PRIOR AUTHORIZATION POLICY

POLICY: Gaucher Disease Substrate Reduction Therapy – Miglustat capsules (Zavesca® – Actelion Pharmaceuticals; generic)

DATE REVIEWED: 05/06/2020

OVERVIEW

Miglustat capsules (Zavesca), a glucosylceramide synthase inhibitor, is indicated as monotherapy for the treatment of adult patients with mild to moderate Gaucher disease type 1 for whom enzyme replacement therapy is not a therapeutic option (e.g., due to allergy, hypersensitivity, or poor venous access).[1] Generic miglustat is an AB-rated therapeutically equivalent generic of Zavesca.

DISEASE OVERVIEW

Gaucher disease is caused by a deficiency in the lysosomal enzyme β-glucocerebrosidase.[2] This enzyme is responsible for the breakdown of glucosylceramide into glucose and ceramide. In Gaucher disease, deficiency of the enzyme β-glucocerebrosidase results in the accumulation of glucosylceramide substrate in lysosomal compartment of macrophages, giving rise to foam cells or "Gaucher cells." Zavesca is a specific inhibitor of the enzyme glycosylceramide synthase, which is responsible for producing the substrate glucosylceramide.[1] By functioning as a substrate reduction therapy, Zavesca allows the residual activity of the deficient glucocerebrosidase enzyme to be more effective.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Zavesca/generic miglustat. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zavesca/generic miglustat as well as the monitoring required for adverse events and long-term efficacy, approval requires Zavesca/generic miglustat to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zavesca/generic miglustat is recommended in those who meet the following criteria:

FDA-Approved Indications

43. Gaucher Disease Type I. Approve for 1 year if Zavesca or generic miglustat is prescribed by or in consultation with a geneticist, endocrinologist, metabolic disorder sub-specialist, or a physician who specializes in the treatment of Gaucher Disease or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Zavesca/generic miglustat has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

108. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

30. Zavesca® [prescribing information]. South San Francisco, CA: Actelion Pharmaceuticals US Inc.; February 2014.
31. Cerdelga™ capsules [prescribing information]. Waterford, Ireland: Genzyme; August 2014.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	New criteria	08/23/2017
Early annual revision	Added generic miglustat to policy with no criteria changes.	05/09/2018
Annual revision	No change to the criteria	05/08/2019
Annual revision	No criteria change	05/06/2020

PRIOR AUTHORIZATION POLICY

POLICY: Gonadotropin-Releasing Hormone Agonist – Synarel Prior Authorization Policy

- Synarel® (nafarelin acetate nasal solution – G.D. Searle LLC)

REVIEW DATE: 11/18/2020

OVERVIEW

Synarel, a gonadotropin-releasing hormone agonist (GnRH), is indicated for the following[1]:

- **Central precocious puberty**, treatment in children of both sexes.
- **Endometriosis management**, including pain relief and reduction of endometriotic lesions. Experience with Synarel for this indication is limited to women ≥ 18 years of age treated for 6 months.

Guidelines

GnRH agonists are the standard of care for the treatment of central precocious puberty is GnRH agonists.[2-4] The European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society convened a consensus conference to review the use of GnRH agonists in pediatric patients with central precocious puberty (2009).[2] The panel noted that the available GnRH agonists (including nafarelin) are effective despite different routes of administration, dosing, and duration of action. In addition, the various GnRH agonists are well-tolerated in children and adolescents. An update by an International Consortium (2019) notes the lack of prospective comparative studies to establish differences in efficacy (if any) among the various GnRH agonists.[3] Discontinuation of GnRH agonist therapy should be individualized, based on the patient's readiness for resumption of puberty, recent growth rates, and shifts in height prediction.

The American College of Obstetrician and Gynecologist (ACOG) practice bulletin on the management of endometriosis (2010, reaffirmed 2018) notes that empiric treatment with a GnRH agonist is appropriate after an appropriate pretreatment evaluation (to exclude other causes of chronic pelvic pain) and failure of initial treatment with oral contraceptives and non-steroidal anti-inflammatory drugs (NSAIDS).[5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Synarel. All approvals are provided for 1 year in duration unless otherwise noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Synarel is recommended in those who meet one of the following criteria:

FDA-Approved Indications

17. Central Precocious Puberty. Approve for 1 year.

18. Endometriosis. Approve for 6 months if the patient meets the following criteria (A and B):

a) Patient is ≥ 18 years of age; AND

b) Patient has tried one of the following, unless contraindicated (i, ii, or iii):

i. A contraceptive; OR
   Note: Examples of contraceptives includes combination oral contraceptives, levonorgestrel-releasing intrauterine systems [e.g., Mirena®, Liletta®]).

ii. An oral progesterone (e.g., norethindrone tablets): OR

iii. A depo-medroxyprogesterone injection
   Note: An exception to the requirement for a trial of the above therapies can be made if the patient has previously used a gonadotropin-releasing hormone (GnRH) agonist (e.g., Lupron Depot) or antagonist (e.g., Orilissa) for endometriosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Synarel is not recommended in the following situations:

3. Peripheral Precocious Puberty (Also Known as Gonadotropin-Releasing Hormone-Independent Precocious Puberty). Children with peripheral precocious puberty do not respond to gonadotropin-releasing hormone agonist therapy.[2] Treatment is directed at removing or blocking the production and/or response to the excess sex steroids, depending on the cause (e.g., surgically removing human chorionic gonadotropin-secreting tumors or using glucocorticoids to treat defects in adrenal steroidogenesis [such as classic congenital adrenal hyperplasia]).

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1 Synarel® [prescribing information]. New York, NY: G.D. Searle LLC, Division of Pfizer Inc.; December 2017.

2 Carel JC, Eugster EA, Rogol A, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics*. 2009;123(4):e752-762.

3 Krishna KB, Fuqua JS, Rogol AD, et al. Use of gonadotropin-releasing hormone analogs in children: update by an international consortium. *Horm Res Paediatr*. 2019;91:357-372.
4 Eugster EA. Treatment of central precocious puberty. *J Endo Soc*. 2019;3:965-972.
5 Management of Endometriosis. ACOG Practice Bulletin. Clinical Management Guidelines for Obstetrician-Gynecologists. Number 114, July 2010. (Reaffirmed 2018) *Obstetrics & Gynecology*. 2010;116(1):223-236.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	11/18/2020

PRIOR AUTHORIZATION POLICY

POLICY: Gonadotropin-Releasing Hormone Agonists – Central Precocious Puberty Prior Authorization Policy

- Fensolvi® (leuprolide acetate for injectable suspension – Tolmar)
- Lupron Depot-Ped® (leuprolide acetate for depot suspension – AbbVie)
- Triptodur™ (triptorelin extended-release injectable suspension – Arbor Pharmaceuticals, LLC)

REVIEW DATE: 09/16/2020

OVERVIEW

Fensolvi, Lupron Depot-Ped, and Triptodur are gonadotropin-releasing hormone (GnRH) agonists indicated for the treatment of children with central precocious puberty.[1-3] Fensolvi is administered by a subcutaneous injection and both Lupron Depot-Ped and Triptodur are administered by intramuscular injection. Fensolvi is administered once every 6 months, Lupron Depot-Ped is administered once a month or once every 3 months, and Triptodur is administered once every 24 weeks.

Guidelines

The standard of care for central precocious puberty is GnRH agonists.[4-6] The European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society convened a consensus conference to review the use of GnRH agonists in pediatric patients with central precocious puberty (2009).[4] The panel noted that the available GnRH agonists (including leuprolide and triptorelin) are effective despite different routes of administration, dosing, and duration of action. In addition, the various GnRH agonists are well-tolerated in children and adolescents. An update by an International Consortium (2019) notes the lack of prospective comparative studies to establish differences in efficacy (if any) among the various GnRH agonists.[5] The Consortium does not prefer one GnRH agonist over another. Discontinuation of GnRH agonist therapy should be individualized, based on the patient's readiness for resumption of puberty, recent growth rates, and shifts in height prediction.

Other Uses With Supportive Evidence

The Endocrine Society Guideline (2017) for the treatment of gender-dysphoric/gender-incongruent persons note that persons who fulfill criteria for treatment and who request treatment should initially undergo treatment to suppress physical changes of puberty.[7] Pubertal hormonal suppression should typically be initiated after the adolescent first exhibits physical changes of puberty (Tanner stages G2/B2). However, there may be compelling reasons to initiate hormone treatment before the age of 16 years in some adolescents. The guidelines note suppression of pubertal development and gonadal function can be effectively achieved via gonadotropin suppression using GnRH analogs. Long-acting GnRH analogs are the currently preferred treatment option. An advantage to using a GnRH analog is that the effects can be

reversed; pubertal suppression can be discontinued if the individual no longer wishes to transition. Upon discontinuation of therapy, spontaneous pubertal development has been shown to resume. The World Professional Association for Transgender Health (WPATH) Standards of Care (version 7) document also recommends the use of GnRH analogs in both male and female adolescents as a fully reversible intervention for pubertal suppression.[8] GnRH can also be used in patients during late puberty to suppress the hypothalamic-pituitary-gonadal axis to allow for lower doses of cross-sex hormones.[9] In addition to use in adolescents, GnRH analog therapy is also used in adults, particularly male-to-female patients.[10]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of gonadotropin-releasing hormone agonists (Fensolvi, Lupron Depot-Ped, and Triptodur). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of gender-dysphoric/gender-incongruent persons treated with Fensolvi, Lupron Depot-Ped, or Triptodur as well as the monitoring required for adverse events and long-term efficacy, approval requires that the product be prescribed by or in consultation with, a physician who specializes in this condition.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of a gonadotropin-releasing hormone agonist (Fensolvi, Lupron Depot-Ped, and Triptodur) is recommended in those who meet the following criteria:

FDA-Approved Indications

12. Central Precocious Puberty. Approve the requested gonadotropin-releasing hormone agonist for 1 year.

Other Uses with Supportive Evidence

13. Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Gender Reassignment (Female-To-Male or Male-To-Female). Approve the requested gonadotropin-releasing hormone agonist for 1 year if prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of transgender patients.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of a gonadotropin-releasing hormone agonist (Fensolvi, Lupron Depot-Ped, and Triptodur) is not recommended in the following situations:

109. Peripheral Precocious Puberty (Also Known as Gonadotropin-Releasing Hormone-Independent Precocious Puberty). Children with peripheral precocious puberty do not respond to gonadotropin-releasing hormone agonist therapy.[4] Treatment is directed at removing or blocking the production and/or response to the excess sex steroids, depending on the cause (e.g., surgically removing human chorionic gonadotropin-secreting tumors or using glucocorticoids to treat defects in adrenal steroidogenesis [such as classic congenital adrenal hyperplasia]).

110. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

272. Lupron Depot-Ped® [prescribing information]. North Chicago, IL; AbbVie, Inc.; May 2017.
273. Triptodur™ [prescribing information]. Atlanta, GA: Arbor Pharmaceuticals, LLC; October 2018.
274. Fensolvi® [prescribing information]. Fort Collins, CO: Tolmar Pharmaceuticals, Inc; May 2020.
275. Carel JC, Eugster EA, Rogol A, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics*. 2009;123(4):e752-762.
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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/17/2018
Selected Revision	• Addition of approval for gender-dysphoric/gender-incongruent persons, persons undergoing gender reassignment. • Changed policy name from Gonadotropin-Releasing Hormone (GnRH) Agonists for Central Precocious Puberty PA Policy with Preferred Step Therapy to Gonadotropin-Releasing Hormone Agonists – Injectable Products (Lupron Depot-Ped and Triptodur) PA Policy with Step Therapy.	03/20/2019
Selected Revision	• Step component for Lupron Depot-Ped for the treatment of central precocious puberty is removed (there is no requirement to try Triptodur first). • Changed policy name from Gonadotropin-Releasing Hormone Agonists – Injectable Products (Lupron Depot-Ped and Triptodur) PA Policy with Step Therapy to Gonadotropin-Releasing Hormone Agonists – Injectable Long-Acting Products (Lupron Depot-Ped and Triptodur) PA Policy.	04/24/2019
Annual Revision	Revised Precocious Precocity (also known as GnRH-independent precocious puberty or peripheral precocious puberty) to Peripheral Precocious Puberty (also known as GnRH-independent precocious puberty).	09/18/2019
Update	11/21/2019: Changed policy name from Gonadotropin-Releasing Hormone Agonists – Injectable Long-Acting Products (Lupron Depot-Ped and Triptodur) PA Policy to Gonadotropin-Releasing Hormone Agonists – Central Precocious Puberty (Lupron Depot-Ped and Triptodur) PA Policy.	NA
Selected Revision	• Added Fensolvi (leuprolide acetate for injectable suspension) to the PA policy. • Changed policy name from Gonadotropin-Releasing Hormone Agonists – Central Precocious Puberty (Lupron Depot-Ped and Triptodur) PA Policy to Gonadotropin-Releasing Hormone Agonists – Central Precocious Puberty (Fensolvi, Lupron Depot-Ped and Triptodur) PA Policy.	05/13/2020
Annual Revision	• Policy name revised from "Gonadotropin-Releasing Hormone Agonists – Central Precocious Puberty (Fensolvi, Lupron Depot-Ped and Triptodur) PA Policy" to "Gonadotropin-Releasing Hormone Agonists – Central Precocious Puberty PA Policy". • No criteria changes.	09/16/2020

NA – Not applicable.

PRIOR AUTHORIZATION POLICY

POLICY: Gonadotropin-Releasing Hormone Agonists Implants Prior Authorization Policy

- Supprelin® LA (histrelin acetate subcutaneous implant – Endo Pharmaceuticals)
- Vantas® (histrelin acetate subcutaneous implant – Endo Pharmaceuticals)

- Zoladex® (goserelin acetate subcutaneous implant – TerSera Therapeutics)

REVIEW DATE: 01/20/2021

Overview

Supprelin LA, Vantas, and Zoladex are gonadotropin-releasing hormone (GnRH) agonists implants.[1-4]

Supprelin LA is indicated for the treatment of children with **central precocious puberty**.[1]

Vantas is indicated for the palliative treatment of **advanced prostate cancer**.[2] Although Vantas is not indicated for use in children with central precocious puberty, it contains the same chemical entity as that of Supprelin LA, and can be used for this condition.

Zoladex is indicated for the following conditions:[3,4]

- **Breast cancer**, palliative treatment of advanced breast cancer in pre- and perimenopausal women (Zoladex 3.6 mg implant only).
- **Endometrial-thinning**, use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding (Zoladex 3.6 mg implant only).
- **Endometriosis**, including pain relief and reduction of endometriotic lesions for the duration of therapy (Zoladex 3.6 mg implant only).
- **Prostate cancer**, in combination with flutamide for the management of locally confined Stage T2b-T4 (Stage B2-C).
- **Prostate cancer**, palliative treatment.

Guidelines

The NCCN Breast Cancer guidelines (version 6.2020 – September 8, 2020) does not note the use of Zoladex implants for advanced breast cancer.[5] However, the guidelines note that GnRH agonists (e.g., Zoladex) administered prior to initiating chemotherapy protect against ovarian failure and reduce the risk of early menopause.

Central precocious puberty, also known as gonadotropin-dependent precocious puberty, is caused by early maturation of the hypothalamic-pituitary-gonadal axis.[6] The standard of care for central precocious puberty is GnRH agonists. The European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society convened a consensus conference (2009) to review the use of GnRH agonists in pediatric patients with central precocious puberty.[7] The panel noted that the available GnRH agonists (including leuprolide, triptorelin, and histrelin implant) are effective despite different routes of administration, dosing, and duration of action. An update by the International Consortium (2019) reiterates the use of GnRH agonists (e.g., leuprolide, triptorelin, and histrelin implant) for the treatment of central precocious puberty.[8] GnRH agonists are generally well-tolerated in children and adolescents.

The National Comprehensive Cancer Network (NCCN) Prostate Cancer guidelines (version 3.2020 – November 17, 2020) list both Vantas and Zoladex as androgen deprivation therapy (ADT) options for use in various settings (all category 2A): clinically localized disease, regional disease, prostate specific antigen (PSA) persistence/recurrence after radical prostatectomy (RP) or external beam radiation therapy (EBRT) [castration-naïve disease], and metastatic castration-naïve disease.[9]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Supprelin LA, Vantas, and Zoladex. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vantas, and Zoladex as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated. Note that as with Supprelin LA, when Vantas is prescribed for use in children with central precocious puberty, it does not need to be prescribed by or in consultation with a specialist.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Vantas is recommended in patients who meet the following criteria:

FDA-Approved Indications

1. **Prostate Cancer.** Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

2. **Central Precocious Puberty.** Approve for 1 year.

II. Coverage of Supprelin LA is recommended in patients who meet the following criteria:

FDA-Approved Indications

1. **Central Precocious Puberty.** Approve for 1 year.

III. Coverage of Zoladex is recommended in patients who meet one of the following criteria:

FDA-Approved Indications

1. **Abnormal Uterine Bleeding.** Approve for up to 2 months (total) if the patient meets the following conditions (A and B):
   A) Zoladex is used as an endometrial-thinning agent prior to endometrial ablation; AND
   B) The medication is prescribed by or in consultation with an obstetrician-gynecologist or a healthcare practitioner who specializes in the treatment of women's health.

2. **Breast Cancer**. Approve for 1 year if the patient meets the following conditions (A and B):
   A) Zoladex is used in premenopausal or perimenopausal women; AND
   B) The medication is prescribed by or in consultation with an oncologist.

3. **Endometriosis.** Approve for up to 6 months (total) if the patient meets the following conditions (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) The medication is prescribed by or in consultation with an obstetrician-gynecologist or a healthcare practitioner who specializes in the treatment of women's health.

4. **Prostate Cancer**. Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Supprelin LA, Vantas, and Zoladex is not recommended in the following situations:

111. Peripheral Precocious Puberty (also known as GnRH-independent precocious puberty).
Children with peripheral precocious puberty do not respond to GnRH agonist therapy.[8] Treatment is directed at removing or blocking the production and/or response to the excess sex steroids, depending on the cause (e.g.,

surgically removing human chorionic gonadotropin-secreting tumors or using glucocorticoids to treat defects in adrenal steroidogenesis [such as classic congenital adrenal hyperplasia]).

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	04/03/2019
Selected Revision	Revised Precocious Puberty (also known as Gonadotropin-releasing hormone independent precocious puberty or peripheral precocious puberty) to Peripheral Precocious Puberty (also known as GnRH-independent precocious puberty).	09/18/2019
Update	11/21/2019: Changed policy name from Gonadotropin-Releasing Hormone Agonists – Supprelin LA, Vantas, Zoladex Implants Prior Authorization Policy to Gonadotropin-Releasing Hormone Agonists – Implants (Supprelin LA, Vantas, and Zoladex) Prior Authorization Policy	NA
Early Annual Revision	No criteria changes. Policy Statement: Removed Supprelin LA from this sentence: Because of the specialized skills required for evaluation and diagnosis of patients treated with Vantas, and Zoladex as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated (Supprelin LA was erroneously included). Approval of Central Precocious Puberty does not require that it be prescribed by or in consultation with a specialist).	01/15/2020
Selected Revision	Vantas: Added approval for central precocious puberty – approve for 1 year. Policy Statement: Added this sentence: Note that as with Supprelin LA, when Vantas is prescribed for use in children with central precocious puberty, it does not need to be prescribed by or in consultation with a specialist.	03/11/2020
Update	09/22/2020: Revised policy name from "Gonadotropin-Releasing Hormone Agonists – Implants (Supprelin LA, Vantas, and Zoladex) PA Policy" to "Gonadotropin-Releasing Hormone Agonists – Implants PA Policy".	NA
Annual Revision	No criteria changes.	01/20/2021

NA – Not applicable.

PRIOR AUTHORIZATION POLICY

POLICY: Gonadotropin-Releasing Hormone Agonists – Injectable Long-Acting Products Prior Authorization Policy

- Lupaneta Pack® (leuprolide acetate for depot suspension; norethindrone acetate tablets co-packaged for intramuscular use and oral use, respectively – AbbVie)
- Lupron Depot® (leuprolide acetate suspension for intramuscular injection – Abbott Laboratories)

REVIEW DATE: 01/20/2021; Selected revision 03/03/2021

Overview

Lupaneta Pack is indicated for initial management of the painful symptoms of **endometriosis** and for management of recurrence of symptoms.[1,2]

Lupron Depot (3.75 mg intramuscular (IM) injection every month, 11.25 mg IM injection every 3 months) is indicated for the following conditions:[3,4]

- Preoperative hematologic improvement of women with **anemia caused by uterine leiomyomata** (fibroids) for whom 3 months of hormonal suppression is deemed necessary. (Lupron Depot in combination with iron therapy).
- **Endometriosis**, including pain relief and reduction of endometriotic lesions (Lupron Depot monotherapy).
- **Endometriosis**, initial management of the painful symptoms of endometriosis and management of recurrence of symptoms (Lupron Depot in combination with norethindrone acetate 5 mg daily).

Lupron Depot (7.5 mg IM injection every month, 22.5 mg IM injection every 3 months, 30 mg IM injection every 4 months, and 45 mg IM injection every 6 months) is indicated for the **palliative treatment of advanced prostate cancer**.[5]

Duration of Treatment:

- Lupaneta Pack: Initial treatment course is limited to 6 months; a single retreatment course of up to 6 months is allowed. Total duration of treatment is limited to 12 months.[1,2]
- Lupron Depot 3.75 mg and 11.25 mg:[3,4]
  - Endometriosis: For the first 6 months of treatment, Lupron Depot may be used as monotherapy or in combination with norethindrone acetate. If retreatment is needed, Lupron Depot must be used in combination with norethindrone acetate (for 6 months). Total duration of treatment is limited to 12 months.
  - Uterine leiomyomata (fibroids): Recommended duration of treatment is up to 3 months.
- Lupron Depot 7.5 mg, 22.5 mg, 30 mg, and 45 mg: Labeling does not specify a treatment duration.

Guidelines

Abnormal Uterine Bleeding/Uterine Leiomyomata (Fibroids)

The American College of Obstetricians and Gynecologists (ACOG) practice bulletin regarding the diagnosis of abnormal uterine bleeding in reproductive-aged women discusses the nomenclature of abnormal uterine bleeding. It can be classified by the acronym PALM-COEIN (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified) and can be further classified by etiology.[6] The term abnormal uterine bleeding can also be paired with descriptive terms that describe the associated bleeding pattern such as heavy menstrual bleeding or intermenstrual bleeding.

The ACOG frequently asked questions (FAQ) #074 (2018) addresses medication use for the treatment of fibroids.[7] Gonadotropin-releasing hormone (GnRH) agonists are noted as medications that can stop the menstrual cycle and shrink fibroids. GnRH analogs are used as short-term preoperative therapy to reduce uterine and leiomyoma volume; long-term therapy should be limited to patients who have contraindications to other medical or surgical treatments.[8] They can also be used for acute abnormal uterine bleeding with an aromatase inhibitor or antagonist to prevent initial estrogen flare and for the treatment of heavy menstrual bleeding caused by leiomyoma-associated hormonal imbalance.[9]

A clinical practice guideline from the Society of Obstetricians and Gynaecologists of Canada notes that leuprolide acetate or combined hormonal contraception should be considered highly effective in preventing abnormal uterine bleeding when initiated prior to cancer treatment in premenopausal women at risk of thrombocytopenia.[10] The ACOG committee opinion on prevention and management of heavy menstrual bleeding in adolescent patients undergoing cancer treatment lists leuprolide as an option for patients.[11]

Endometriosis

According to the ACOG practice bulletin on the management of endometriosis (2010, reaffirmed 2018), empiric therapy with a 3-month course of a gonadotropin-releasing hormone (GnRH) agonist is appropriate after an appropriate pretreatment evaluation (to exclude other causes of chronic pelvic pain) and failure of initial treatment with oral contraceptives and nonsteroidal anti-inflammatory drugs (NSAIDs).[12]

Other Uses With Supportive Evidence

The Endocrine Society Guideline (2017) for the Treatment of Gender-Dysphoric/Gender-Incongruent Persons note that persons who fulfill criteria for treatment and who request treatment should initially undergo treatment to suppress physical changes of puberty.[13] Pubertal hormonal suppression should typically be initiated after the adolescent first exhibits physical changes of puberty (Tanner stages G2/B2).

However, there may be compelling reasons to initiate hormone treatment before the age of 16 years in some adolescents. The guidelines note suppression of pubertal development and gonadal function can be effectively achieved via gonadotropin suppression using GnRH analogs. Long-acting GnRH analogs are the currently preferred treatment option. An advantage to using a GnRH analog is that the effects can be reversed; pubertal suppression can be discontinued if the individual no longer wishes to transition. Upon discontinuation of therapy, spontaneous pubertal development has been shown to resume. The World Professional Association for Transgender Health (WPATH) Standards of Care (version 7) document also recommends the use of GnRH analogs in both male and female adolescents as a fully reversible intervention for pubertal suppression.[14] GnRH can also be used in patients during late puberty to suppress the hypothalamic-pituitary-gonadal axis to allow for lower doses of cross-sex hormones.[15] In addition to use in adolescents, GnRH analog therapy is also used in adults, particularly male-to-female patients.[16]

In addition to the approved indications, GnRH agonists such as long-acting leuprolide, have been used for other conditions. The National Comprehensive Cancer Network (NCCN) guidelines for Adolescent and Young Adult Oncology (version 1.2021 – September 10, 2020) note there are some data to suggest menstrual suppression with GnRH agonists (before the initiation of chemotherapy) may protect ovaries in young women with breast cancer.[17] There are conflicting data regarding the beneficial effects of GnRH agonists on fertility preservation. The NCCN guidelines for Breast Cancer (version 6.2020 – September 8, 2020) note that luteinizing hormone-releasing hormone agonists, such as leuprolide, can be used for ovarian suppression.[18] The guidelines further note that randomized trials have shown that ovarian suppression with GnRH agonist therapy administered during adjuvant chemotherapy in premenopausal women with breast tumors (regardless of hormone receptor status) may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhea. The NCCN guidelines for Head and Neck Cancer (version 1.2021 – November 9, 2020) recommend the use of androgen receptor therapy (i.e., leuprolide, bicalutamide) for androgen receptor-positive, advanced salivary gland tumors with distant metastases.[19] The NCCN guidelines for Ovarian Cancer including Fallopian Tube Cancer and Primary Peritoneal Cancer (version 2.2020 – January 12, 2021) recommend leuprolide as a hormonal therapy option in various settings (e.g., adjuvant therapy, recurrence).[20]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lupaneta Pack and Lupron-Depot. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lupaneta Pack and Lupron-Depot as well as the monitoring required for adverse events and long-term efficacy, approval for some of the conditions requires Lupaneta Pack and Lupron-Depot to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

Recommended Authorization Criteria

Coverage of Lupaneta Pack and Lupron Depot is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Endometriosis.** Approve Lupron Depot or Lupaneta Pack for 1 year if the patient has tried one of the following (A, B, or C):
   - **A)** A contraceptive (e.g., combination oral contraceptives, levonorgestrel-releasing intrauterine systems [e.g., Mirena®, Liletta®]), OR
   - **B)** An oral progesterone (e.g., norethindrone tablets), OR

C) A depo-medroxyprogesterone injection, unless contraindicated.
NOTE: An exception to the requirement for a trial of the above therapies can be made if the patient has previously used a gonadotropin-releasing hormone [GnRH] agonist (e.g., Lupron-Depot) or antagonist (e.g., Orilissa).

2. **Prostate Cancer.** Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.

3. **Uterine Leiomyomata (fibroids).** Approve Lupron Depot for 3 months.

Other Uses with Supportive Evidence

4. **Abnormal Uterine Bleeding.** Approve Lupron Depot for 6 months.

5. **Breast Cancer.** Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.

6. **Gender Dysphoric/Gender-Incongruent Persons; Persons Undergoing Gender Reassignment (Female-To-Male [FTM] or Male-To-Female [MTF]).** Approve Lupron Depot for 1 year if prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of transgender patients.

7. **Head and Neck Cancer – Salivary Gland Tumors.** Approve Lupron Depot for 1 year if the patient meets the following criteria (A, B, and C):
   A) Patient has advanced salivary gland tumors with distant metastases; AND
   B) Patient has androgen receptor (AR)-positive disease; AND
   C) The medication is prescribed by or in consultation with an oncologist.

8. **Ovarian Cancer.** Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.

9. **Preservation of Ovarian Function/Fertility in Patients Undergoing Chemotherapy.** Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.

10. **Prophylaxis or Treatment of Uterine Bleeding in Patients with Hematologic Malignancy, or Undergoing Cancer Treatment, or Prior to Bone Marrow/Stem Cell Transplantation (BMT/SCT).** Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lupron Depot and Lupaneta Pack is not recommended in the following situations:

1. **Hirsutism.** The Endocrine Society guidelines (2018) on the treatment of hirsutism in premenopausal women suggest against using GnRH agonists except in women with severe forms of hyperandrogenemia, such as ovarian hyperthecosis, who have had a suboptimal response to oral contraceptives and antiandrogens.[21]

2. **Menstrual Migraine.** A review article notes that GnRH analogs are effective in eliminating menstrual migraines, but their use is limited due to the significant adverse effects of estrogen deficiency, including severe vasomotor symptoms, sleep disruption, and a marked reduction in bone density.[22,23]

3. **Premenstrual Syndrome (PMS).** On occasion, GnRH analogs are recommended as an aid in the diagnosis of PMS.[24] Use of GnRH analogs results in profound cycle suppression and elimination of PMS symptoms, but these agents should not be used routinely. GnRH analogs are recommended only as a third-line treatment or for the most refractory patients.

4. **Polycystic Ovarian Syndrome (PCOS).** PCOS guidelines from the Endocrine Society (2013)[25] and review articles[26,27] do not recommend this as a treatment modality.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	• Removal of Lupron Depot-Ped and Triptodur and the indication of central precocious puberty. These medications are addressed in the policy: Gonadotropin-Releasing Hormone Agonists for Central Precocious Puberty PA Policy with Preferred Step Therapy. • Updated the following indication, Prophylaxis or Treatment of Uterine Bleeding in Patients with Hematologic Malignancy or Prior to Bone Marrow/Stem Cell Transplantation to include patients undergoing cancer treatment. • Added "if prescribed by or in consultation with an oncologist" to the following diagnoses: Prostate Cancer, Ovarian Cancer, Breast Cancer, Preserve Ovarian Function/Fertility in Patients undergoing Chemotherapy, and Prophylaxis or Treatment of Uterine Bleeding in Patients with Hematologic Malignancy or Undergoing Cancer Treatment, or Prior to Bone Marrow/Stem Cell Transplantation to align with the Lupron Depot Medical Benefit Management policy.	1/30/2019
Selected Revision	• Updated endometriosis criterion: removal of continued pain criteria and removal of prescriber's specialty or consultation specialty. • Added the wording Gender Dysphoric/Gender Incongruent Persons to the diagnosis for Gender Reassignment.	4/10/2019
Annual Revision	No criteria changes.	01/15/2020
Update	09/22/2020: Revised policy name from "Gonadotropin-Releasing Hormone Agonists – Injectable Long-Acting Products (Lupron Depot and Lupaneta Pack) Prior Authorization Policy" to "Gonadotropin-Releasing Hormone Agonists – Injectable Long-Acting Products Prior Authorization Policy".	--
Annual Revision	Head and Neck Cancer – Salivary Gland Tumors: revised "Patient has recurrent disease with distant metastases" to "Patient has advanced salivary gland tumors with distant metastases".	01/20/2021
Selected Revision	Lupron Depot 3.75 mg and 11.25 mg – Uterine leiomyomata (fibroids): Approval duration is changed from 6 months to 3 months, due to revised labeling.	03/03/2021

PRIOR AUTHORIZATION POLICY

POLICY: Gonadotropin-Releasing Hormone Antagonists – Oriahnn™ (elagolix, estradiol, and norethindrone acetate capsules; elagolix capsules – AbbVie Inc.)

DATE REVIEWED: 06/03/2020

OVERVIEW

Oriahnn, an oral gonadotropin-releasing hormone (GnRH) receptor antagonist with added estrogen and progestin therapy, is indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women.[1] Oriahnn consists of two capsules: one capsule to be taken in the morning and one capsule to be taken in the evening. The morning capsule contains elagolix 300 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg and the evening capsule contains elagolix 300 mg. Elagolix inhibits endogenous GnRH signaling by binding competitively to GnRH receptors in the pituitary gland. Therapy results in suppression of luteinizing hormone (LH) and follicle stimulating hormone (FSH), decreasing blood concentrations of estradiol and progesterone, and resulting in a hypogonadal state. Estradiol and norethindrone are considered as "add-back" therapy to attenuate side effects of GnRH therapy (i.e., decreased bone mineral density).

Disease Overview

Uterine fibroids (leiomyomas) are benign tumors. They are the most frequent gynecologic benign disease.[2] Fibroids can be asymptomatic or cause symptoms; symptoms generally present as abnormal (heavy) uterine bleeding or pelvic

pain/pressure. Heavy menstrual bleeding can cause associated problems, such as iron deficiency anemia. The actual prevalence of uterine fibroids is difficult to ascertain since many are asymptomatic, but it is estimated that fibroids can be detected in up to 80% of women by 50 years of age.[3]

Guidelines

Oriahnn is not addressed in guidelines for uterine fibroids. There are multiple American College of Obstetricians and Gynecologists (ACOG) guidelines related to leiomyomas (fibroids), but none specific to the management of heavy menstrual bleeding. According to the ACOG guideline, Alternatives to Hysterectomy in the Management of Leiomyomas (2008) [reaffirmed 2019], GnRH agonists have been widely used for preoperative treatment, both for myomectomy and hysterectomy.[4] Guidelines on the Management of Uterine Leiomyomas from the Society of Obstetricians and Gynecologists of Canada (SOGC) [2015] state that effective medical treatments for women with abnormal uterine bleeding associated with uterine fibroids include the levonorgestrel intrauterine system, GnRH analogues, selective progesterone receptor modulators, oral contraceptives, progestins, and danazol.[5]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Oriahnn. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Oriahnn as well as the monitoring required for adverse events and long-term efficacy, approval requires Oriahnn to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Oriahnn is recommended in those who meet the following criteria:

FDA-Approved Indications

33. Heavy Menstrual Bleeding Associated with Uterine Fibroids. Approve for 24 months if the patient meets the following criteria (A, B, C, D, E, and F):

- **A)** The patient is ≥ 18 years of age; AND
- **B)** The patient is premenopausal; AND
- **C)** Uterine fibroids have been confirmed by a pelvic ultrasound, hysteroscopy, or magnetic resonance imaging; AND
- **D)** The patient has tried at least one other therapy for the medical management of heavy menstrual bleeding; AND
  Note: Examples include: combination oral contraceptives, levonorgestrel-releasing intrauterine systems [e.g. Mirena®, Liletta®], an oral progesterone (e.g., medroxyprogesterone acetate), depo-medroxyprogesterone injection, tranexamic acid tablets.
- **E)** The patient has not previously received 24 months or longer of therapy of Oriahnn; AND
- **F)** The medication is prescribed by or in consultation with an obstetrician-gynecologist or a health care practitioner who specializes in the treatment of women's health.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Oriahnn has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

49. Heavy Menstrual Bleeding not associated with Uterine Fibroids.
Oriahnn has been shown effective in reducing heavy menstrual bleeding only in women with uterine fibroids.[1]

50. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

133. Oriahnn™ (elagolix, estradiol, and norethindrone acetate capsules; elagolix capsules), co-packaged for oral use [prescribing information]. North Chicago, IL: AbbVie Inc.; May 2020.
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136. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin. Alternatives to hysterectomy in the management of leiomyomas. 2008 [reaffirmed 2019]. *Obstet Gynecol.* 2008;112:387-400.
137. Vilos GA, Allaire C, Laberge P, et al. The Management of Uterine Leiomyomas. *J Obstet Gynaecol Can.* 2015;37(2):157-178.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	-	6/10/2020

PRIOR AUTHORIZATION POLICY

POLICY: Gonadotropin-Releasing Hormone Antagonists – Orilissa™ (elagolix tablets – AbbVie Inc.)

APPROVAL DATE: 4/01/2020

OVERVIEW

Orilissa is an oral gonadotropin-releasing hormone (GnRH) receptor antagonist indicated for the management of moderate to severe pain associated with endometriosis.[1] In patients with normal liver function or mild hepatic impairment, the recommended dosage is 150 mg once daily for up to 24 months or 200 mg twice daily for up to 6 months. In patients with moderate hepatic impairment (Child-Pugh Class B), the recommended dosage is 150 mg once daily for up to 6 months. The use of 200 mg twice daily dosing is not recommended in patients with moderate hepatic impairment. Orilissa is contraindicated in patients with severe hepatic impairment. Duration of therapy is limited due to the anti-estrogenic effects of the medication which include a decrease in bone mineral density (BMD).

Disease Overview

Endometriosis is a condition where the tissues similar to the lining of the uterus (or endometrium) migrate outside of the womb and are found elsewhere in the body.[2,3] The migrated tissues are generally found in the pelvic cavity (e.g., peritoneum, uterosacral ligaments, rectal-vaginal septum, or any spaces between the bladder, uterus, vagina, and rectum) and can attach to any of the female reproductive organs (e.g., ovaries, fallopian tubes). The migrated tissue is less commonly found outside the pelvic cavity or on the intestines, colon, appendix or rectum. Endometriosis affects an estimated 176 million women of reproductive age worldwide.[3] Many women are not diagnosed and therefore not treated. The most common symptom of endometriosis is pelvic pain. The pain often correlates to the menstrual cycle, but not always. Symptoms can range from minimal to severely debilitating. Many women with endometriosis also experience dyspareunia and infertility.

Guidelines

According to the American College of Obstetrician and Gynecologist (ACOG) practice bulletin on the management of endometriosis (2010, reaffirmed 2018), after an appropriate pretreatment evaluation (to exclude other causes of chronic pelvic pain) and failure of initial treatment with OCs and NSAIDs, empiric therapy with a 3-month course of a GnRH agonist is appropriate.[4]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Orilissa. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: When available, the ICD-9/ICD-10 codes for endometriosis (ICD-9: 617 through 617.9 and ICD-10: N80 through N80.9) **AND** a prior therapy in the last 180 days which includes any one of the following: contraceptives (STCs 0248, 9654, and 9495), intrauterine devices (STC 4730), oral progestins (STC 0246 RT 01), depo-medroxyprogesterone injections (STC 4139), GnRH agonists (STC 8253, STC E851, STC 8254 STR 0190 RT 27), or Orilissa will be used to allow approval of the requested medication.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Orilissa is recommended in those who meet the following criteria:

FDA-Approved Indications

44. Endometriosis. Approve for the duration noted if the patient meets one of the following (A or B):

35. Initial Therapy. Approve for 6 months if the patient has tried one of the following: a contraceptive (e.g., combination oral contraceptives, levonorgestrel-releasing intrauterine systems [e.g., Mirena®, Liletta®]), an oral progesterone (e.g., norethindrone tablets), or a depo-medroxyprogesterone injection, unless contraindicated; OR

NOTE: An exception to the requirement for a trial of the above therapies can be made if the patient had previously used a gonadotropin-releasing hormone agonist (e.g., Lupron Depot®) for endometriosis.

36. Patients Continuing Therapy. Approve for 6 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Orilissa has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

177. Orilissa™ tablets for oral use [prescribing information]. North Chicago, IL: AbbVie Inc.; August 2019.
178. Endometriosis. Endometriosis Foundation of America. Accessed on March 26, 2020. Available at https://www.endofound.org/endometriosis.
179. Global Forum. Endometriosis.org. Accessed on March 26, 2020. Available at http://endometriosis.org/endometriosis/.
180. Management of Endometriosis. ACOG Practice Bulletin. Clinical Management Guidelines for Obstetrican-Gynecologists. Number 114, July 2010. (Reaffirmed 2018) *Obstetrics & Gynecology.* 2010; 116(1): 223-236.

HISTORY

Type of Revision	Summary of Changes	Approval Date
New Policy	--	08/08/2018
Selected revision	Removed trial of non-steroidal anti-inflammatory NSAID from criteria.	10/3/2018
Early annual revision	Addition of automation to the policy for the diagnosis of endometriosis and prior medications used for endometriosis. Removal of continued pain criteria and prescriber's specialty or consultation specialty. Removal of select continuation criteria and conditions not recommended for approval.	4/10/2019
Annual revision	No changes	4/01/2020

PRIOR AUTHORIZATION POLICY

POLICY: Gout – Krystexxa® (pegloticase injection for intravenous [IV] infusion – Savient Pharmaceuticals)

DATE REVIEWED: 04/29/2020

OVERVIEW

Krystexxa is a PEGylated uric acid specific enzyme indicated for treatment of chronic gout in adult patients refractory to conventional therapy.[1-2] It is made up of a recombinant modified mammalian uricase produced by a genetically modified strain of *Escherichia coli* which is covalently bonded to monomethoxypoly (ethylene glycol) [mPEG].[1] The recommended dose of Krystexxa is 8 mg administered every 2 weeks over no less than 120 minutes as an intravenous (IV) infusion. Before beginning therapy with Krystexxa, it is recommended that all oral urate-lowering therapies (ULTs) are discontinued and not restarted while on Krystexxa because concomitant use may blunt any increase in serum uric acid (SUA) levels.

Disease Overview

Gout results from a metabolic disorder called hyperuricemia caused by an overproduction or underexcretion of uric acid. Hyperuricemia is typically defined as a serum uric acid level greater than 6.8 mg/dL; however, asymptomatic patients with elevated uric acid levels do not have gout and do not require treatment.[10-11] Excessive amounts of uric acid in the blood lead to deposits of crystals in the joints and connective tissues and may cause excruciating pain. Lumps of urate crystals (tophi) may develop in soft tissues such as the elbow, ear, or distal finger joints. Treatment-failure gout (TFG) exists in a small population of patients with severe gout.[5] These patients have failed to normalize SUAand have inadequate control of the signs and symptoms of gout with maximum medically appropriate doses of ULT (e.g., allopurinol, Uloric) or have a contraindication to ULT. TFG should be differentiated from gout in patients who are under-treated for gout or are non-compliant with gout therapy. Those with TFG generally have a high prevalence of tophi, frequent and disabling gout flares, deforming arthropathy, diminished quality of life, and disability.[2] TFG commonly co-exists with other conditions, including hypertension, cardiovascular disease (CVD), diabetes mellitus, chronic kidney disease, obesity, and hyperlipidemia. Although many patients with gout have concomitant cardiovascular (CV) co-morbidities, it is unknown if elevated SUA is a predictor or causative factor associated with CVD.[6] Of the estimated 5 million patients in the US with gout, it is believed that TFG affects approximately 50,000 patients,[2] although some reports indicate that as many as 300,000

patients may be afflicted.[5] Krystexxa achieves a therapeutic effect by catalyzing the oxidation of uric acid to allantoin.[1] Allantoin is then eliminated, mainly by renal excretion, thus lowering serum uric acid (SUA).

Guidelines

The American College of Rheumatology (ACR) guidelines (2012) for the management of gout have not been updated since the FDA required the labeling of Uloric to have a new Boxed Warning and updated indication due to increased risk of death compared with allopurinol.[7-8] Although Uloric was previously approved for use in the first-line setting of gout, it is now labeled for use only following maximal titration of allopurinol, or an intolerance or inability to use allopurinol.[8-9] ACR guidelines (developed when Uloric was indicated for hyperuricemia in patients with gout) recommend xanthine oxidase inhibitors, either allopurinol or Uloric® (febuxostat tablets), as first-line pharmacologic ULT.[3] Serum urate level should be lowered sufficiently to improve the signs and symptoms of gout and may require therapeutic serum urate level lowering to below 5 mg/dL. Probenacid is recommended as an alternative first-line pharmacologic therapy if the patient had intolerance or contraindications to at least one first-line agent but is not recommended as first-line monotherapy in patients with estimated creatinine clearance (CrCl) < 50 mL/min. In patients with refractory disease, effective therapeutic options include combination therapy with a xanthine oxidase inhibitor and a uricosuric agent (e.g., probenacid, fenofibrate, or losartan). While Krystexxa is never recommended as first-line therapy, it is appropriate in patients with severe gout disease burden and refractoriness to, or intolerance of, appropriately dosed oral ULTs.

The European League Against Rheumatism (EULAR) has recommendations for gout (2016).[4] In patients with normal renal function, allopurinol is recommended as first-line ULT. The allopurinol dose should be adapted to the patient's renal function and slowly titrated to the maximum allowed dosage. If the target SUA is not achieved, the guidelines recommend switching to a uricosuric ±-allopurinol or Uloric. In patients who do not achieve target SUA, combined therapy with a uricosuric + XOI is recommended. Krystexxa is recommended only in patients with crystal-proven severe, debilitating gout, in patients with poor quality of life, when the target SUA cannot be reached with any other available drug (including combinations) at the maximal dose.

Other Uses with Supportive Evidence

Nephrolithiasis and/or Gouty Nephropathy

Approximately 10% to 20% of patients with primary gout will develop kidney stones, with factors such as diet and genetic aspects playing a role in their development.[11] However, the most common reason for the development of uric acid nephrolithiasis has no identifiable secondary cause for the development of uric acid stones. Even though clinical gout is not present, the condition resembles primary gout in many aspects, including a persistently low urine pH, a reduced fractional excretion of uric acid, and varying degrees of hyperuricemia.

Safety

Krystexxa has Boxed Warnings due to concerns of anaphylaxis and infusion reactions.[1] Krystexxa should be administered in a healthcare setting by a healthcare professional. Patients should be pre-medicated with corticosteroids and antihistamines. Anaphylaxis may occur with any infusion, including the first infusion. Systems of anaphylaxis generally manifest within 2 hours of the infusion; delayed-type hypersensitivity reactions have also been reported. The risk of anaphylaxis and infusion reactions are higher in patients whose uric acid level increases to above 6 mg/dL, particularly when two consecutive levels above 6 mg/dL are observed. There is also a Boxed Warning concerning hemolysis and methemoglobinemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Krystexxa. Because of the specialized skills required for evaluation and diagnosis of patients treated with Krystexxa as well as the monitoring required for adverse events (AEs) and efficacy, approval requires Krystexxa to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Krystexxa is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Gout, Chronic.** Approve for the duration noted below if the patient meets ONE of the following conditions (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Krystexxa is prescribed by or in consultation with a rheumatologist or a nephrologist; AND
     - **ii.** The patient meets one of the following conditions (a or b):
       - **a)** The patient has had an inadequate response, defined as a serum uric acid level that remained > 6 mg/dL following a 3-month trial of at least ONE of the following agents: allopurinol, Uloric, or a uricosuric agent.
         Note: Examples of uricosuric agents include probenecid, fenofibrate, and losartan;OR
       - **b)** The patient has a contraindication or has had an intolerance to a trial of allopurinol, as determined by the prescribing physician; AND
     - **iii.** Patient has current symptoms of gout.
       Note: Examples of gout symptoms include gout flares, gout tophus, and gouty arthritis.
   - **B)** Patients currently receiving Krystexxa. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Krystexxa is prescribed by or in consultation with a rheumatologist or a nephrologist; AND
     - **ii.** The patient is continuing therapy with Krystexxa to maintain response/remission; AND
     - **iii.** Patient has responded to therapy with evidence of serum uric acid level < 6 mg/dL with continued Krystexxa treatments.

Other Uses with Supportive Evidence

2. **Nephrolithiasis and/or Gouty Nephropathy.** Approve for the duration noted below if the patient meets ONE of the following conditions (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets BOTH of the following conditions (i and ii):
     - **i.** Krystexxa is prescribed by or in consultation with a rheumatologist or a nephrologist; AND
     - **ii.** Patient meets one of the following conditions (i or ii):
       - **a)** Patient has had an inadequate response, defined as a serum uric acid level that remained > 6 mg/dL following a 3-month trial of allopurinol or Uloric; OR
       - **b)** Patient has a contraindication or has had an intolerance to a trial of allopurinol, as determined by the prescribing physician.
   - **B)** Patients Currently Receiving Krystexxa. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Krystexxa is prescribed by or in consultation with a rheumatologist or a nephrologist; AND
     - **ii.** The patient is continuing therapy with Krystexxa to maintain response/remission; AND
     - **iii.** Patient has responded to therapy with evidence of serum uric acid level < 6 mg/dL with continued Krystexxa treatments.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Krystexxa has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

7. **Known Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency.** Because of risks of hemolysis and methemoglobinemia, Krystexxa is contraindicated in G6PD deficiency.[1] Patients at increased risk of this deficiency (e.g., those of African or Mediterranean ancestry) should be screened prior to initiation of therapy.

8. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Krystexxa™ injection for intravenous infusion [prescribing information]. East Brunswick, NJ: Savient Pharmaceuticals; July 2018.
2. Sundy JS, Baraf HS, Yood RA, et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. *JAMA*. 2011;306(7):711-720.
3. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology Guidelines for management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res.* 2012;64:1431-1446.
4. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis.* 2017;76(1):29-42.
5. Edwards NL. Treatment-failure gout: a moving target. *Arthritis Rheum*. 2008;58(9):2587-2590.
6. Marasini B, Massarotti M. What rheumatologists should know about gout and cardiovascular disease. *J Rheumatol*. 2009;36(4):854-855.
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8. Assadi F. Managing new-onset gout in pediatric renal transplant recipients: when, how, to what extent. *J Nephrol*. 2013;26(4):624-628.
9. Wiederkehr MR, Moe OW. Uric Acid Nephrolithiasis: a systemic metabolic disorder. *Clin Rev Bone Miner Metab*. 2011;9(3-4):207-217.
10. Shen Z, Rowlings C, Kerr B, et al. Pharmacokinetics, pharmacodynamics, and safety of lesinurad, a selective uric acid reabsorption inhibitor, in healthy adult males. *Drug Des Devel Ther*. 2015;9:3423-3434
11. Gout. Centers for Disease Control and Prevention [Web site]. Last reviewed January 28, 2019. Available at: http://www.cdc.gov/arthritis/basics/gout.html. Accessed on April 21, 2020.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual revision	No criteria changes.	10/11/2018
Early annual revision	Early revision to align with review date for new MBM Policy. **Gout, Chronic:** Due to the updated indication and Boxed Warning for Uloric, criteria were changed to require one of the listed therapies (previously required two therapies). The exception for patients who have a contraindication or intolerance to both allopurinol and Uloric was changed to only apply to allopurinol. Additionally, reference to Zurampic and Duzallo were removed from the policy (no longer available). **Nephrolithiasis and/or Gouty Nephropathy:** The exception for patients who have a contraindication or intolerance to both allopurinol and Uloric was changed to only apply to allopurinol.	04/24/2019
Annual revision	**Gout, Chronic:** Clarify in criteria that an inadequate response to previous therapy is defined by serum uric acid (SUA) level that remains > 6 mg/dL (previously SUA level was listed as an i.e. in the criteria). Examples uricosuric agents were moved to a Note in the criteria section (previously listed within the criteria). Examples of gout symptoms were moved to a note (previously included within the criteria). For patients continuing therapy, remove criterion that generally require that the patient has previously responded to Krystexxa (not needed because criteria also require a specific response, defined as evidence of serum uric acid level < 6 mg/dL with Krystexxa). **Nephrolithiasis and/or Gouty Nephropathy:** Clarify in criteria that an inadequate response to previous therapy is defined by serum uric acid (SUA) level that remains > 6 mg/dL (previously SUA level was listed as an i.e. in the criteria). For patients continuing therapy, remove criterion that generally require that the patient has previously responded to Krystexxa (not needed because criteria also require a specific response, defined as evidence of serum uric acid level < 6 mg/dL with Krystexxa).	04/29/2020

PRIOR AUTHORIZATION POLICY

POLICY: Growth Disorders – Growth Hormone [somatropin] Prior Authorization Policy

- Genotropin®(somatropin injection – Pfizer)
- Humatrope® (somatropin injection – Eli Lilly)
- Norditropin® (somatropin injection – Novo Nordisk)
- Nutropin AQ® (somatropin injection – Genentech)
- Omnitrope® (somatropin injection – Sandoz)
- Saizen® (somatropin injection – EMD Serono)
- Serostim® (somatropin injection – EMD Serono)
- Zomacton™ (somatropin injection – Ferring Pharmaceuticals)
- Zorbtive® (somatropin injection – EMD Serono)

REVIEW DATE: 02/10/2021

OVERVIEW

Indications for somatropin vary among these products. Somatropin is indicated for the following conditions:

- **Growth failure, treatment of pediatric patients**, due to an inadequate secretion of endogenous growth hormone.[1-7]
- **Non-growth hormone deficient short stature (idiopathic short stature)**, treatment, defined by height standard deviation score (SDS) ≤ -2.25 (1.2 percentile), and associated with growth rates unlikely to permit attainment of adult height in the normal range.[1-4,6,7]
- **Adults with growth hormone deficiency (GHD)** for replacement of endogenous growth hormone.[1-7]

- **Children with chronic kidney disease (CKD)**, treatment of growth failure, up to the time of kidney transplantation.[4]
- **Noonan syndrome**, treatment of patients with short stature.[3]
- **Prader Willi syndrome**, treatment of patients with growth failure or short stature.[1,3,7]
- **Short stature homeobox-containing gene (SHOX) deficiency**, treatment of short stature or growth failure in children.[2,6]
- **Small for gestational age (SGA)**, treatment of growth failure or short stature in patients with no catch-up growth by age 2[1,7] to 4 years[2,3,6].
- **Turner syndrome**, treatment of short stature.[1-4,6,7]
- **Short bowel syndrome (SBS)**, treatment, in adult patients receiving specialized nutritional support.[8]
- **Human immunodefiency virus (HIV) infected patients with wasting or cachexia**, treatment, to increase lean body mass (LBM) and body weight, and improve physical endurance.[9]

Growth Hormone Deficiency in Children and Adolescents

Somatropin is indicated for the treatment of growth failure in children due to an inadequate secretion of endogenous growth hormone.[1-7] In these children with GHD, somatropin is effective for increasing final adult height.[31] Somatropin therapy is recommended to normalize adult height and avoid extreme shortness in children and adolescents with GHD.[31] Cranial radiation often causes hypopituitarism, and GHD is a frequent pituitary abnormality seen in children and adults who have undergone cranial radiation.[17] Children who have undergone total body irradiation in preparation for hematopoietic stem cell transplant commonly have GHD and an impaired growth rate; these patients can be treated successfully with growth hormone.[-] Somatropin therapy improves the final height of young children after total body irradiation.[11]

Congenital Hypopituitarism

Somatropin is used in infants and young children with congenital hypopituitarism, that manifests in infancy with hypoglycemia, microgenitalia, hyperbilirubinemia, and multiple anterior pituitary hormone deficiencies.[31] The Pediatric Endocrine Society guidelines suggest that GHD due to congenital hypopituitarism be diagnosed without formal growth hormone provocative testing in a newborn with hypoglycemia who does not attain a serum growth hormone concentration > 5 mcg/L (> 5 ng/mL) and has deficiency of at least one additional pituitary hormone and/or the classical imaging triad (ectopic posterior pituitary and pituitary hypoplasia with abnormal stalk).[31]

Non-Growth Hormone Deficient Short Stature (Idiopathic Short Stature) in Children or Adolescents

Somatropin is indicated for the long-term treatment of idiopathic short stature (non-growth hormone deficient short stature) which is defined by a height SDS > 2.25 (1.2 percentile) and associated with growth rates that are unlikely to permit attainment of adult height in the normal range.[1-4,6,7] The predicted adult heights of these children was < 160 cm (63 inches) for men and < 150 cm (59 inches) in women.[31] The Pediatric Endocrine Society guidelines[31] recommend that the decision to treat idiopathic short stature with somatropin be made on a case-by-case basis after assessing physical and psychological burdens, and discussion of risks and benefits. They recommend against the routine use of somatropin in every child with height SDS ≤ -2.25. In one consensus statement on children with idiopathic short stature from the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop, it was felt that the optimal age for initiating treatment is 5 years to early puberty.[12]

The initial 6-month trial of somatropin is to establish that the child's condition responds to somatropin therapy. Authorization for continued therapy should be based on an adequate clinical response[14] defined as an annualized growth rate that doubles in comparison to the previous year. Children who show a striking

increase in growth velocity during the first 6 to 12 months of somatropin therapy are most likely to benefit from long-term therapy, and therapy should be discontinued if there is no significant increase in growth rate during the first year. Children who have a significant increase in growth rate after the first 6-month trial and the next 12 months should then be reviewed annually for growth rate, closure of the epiphyses, and/or attainment of mid-parental height.

Growth Hormone Deficiency in Adults or Transition Adolescents

Somatropin is indicated for the replacement of endogenous growth hormone in adults with GHD, which may present in adults or children as GHD (isolated GHD) or in addition to other pituitary hormone deficiencies (gonadotropin, adrenocorticotropic hormone [ACTH], and/or thyroid-stimulating hormone [TSH] deficiencies).[15] Patients with other anterior pituitary hormone deficiencies are likely to have GHD. In adults, the diagnosis of GHD usually is made in patients with signs and symptoms of hypothalamic-pituitary disease (endocrine, structural, and/or genetic causes); those who have received cranial irradiation or tumor treatment; or those with traumatic brain injury or subarachnoid hemorrhage.[15,16] Onset may be in adulthood or childhood. In childhood, the goal of somatropin therapy is primarily for statural growth. When final adult height is attained, somatropin therapy is no longer required for statural growth. Transition is used to describe the period in adolescence after growth is completed and the need for continued replacement into adulthood is assessed. Ongoing GHD is most likely in patients with multiple pituitary hormone deficits, with or without structural pituitary or peripituitary disease, and/or a history of cranial radiation therapy. Confirmatory growth hormone stimulation testing may not be required in patients, such as with congenital/genetic GHD or multiple pituitary hormone deficiencies. When persistent GHD is documented after completion of adult height, somatropin therapy should be continued to attain full skeletal and muscle maturation during the transition period from childhood to adulthood.[15] In adults with GHD, somatropin replacement therapy improves abnormalities in substrate metabolism, body composition, and physical and psychosocial function.[15,16]

Growth hormone is not approved by the FDA for the treatment of other conditions in adults who may have a low growth hormone response to growth hormone provocative testing (such as obesity, aging, or depression) or to improve athletic performance.[17,18]

Growth Hormone Stimulation Tests (Adults or Transition Adolescents)

The insulin tolerance test is the gold standard growth hormone stimulation test,[53] but is contraindicated in patients with ischemic heart disease or seizure disorders or in elderly or pregnant patients.[15,16,27] The glucagon stimulation test and the macimorelin test could be considered as alternatives test.[53] The response to all growth hormone stimulation tests show intra-individual variability, and the growth hormone cutoff points vary with the test used. Otherwise healthy obese persons have blunted growth hormone responses to various tests.[30] There is no information on the effects of increased body mass index (BMI) or central adiposity on the insulin tolerance test. When Geref was available [discontinued in the US in 2008], Geref (GHRH) plus arginine was considered the best alternative to the insulin tolerance test in adults.

Macrilen (macimorelin) is the most recently approved test for the diagnosis of adult GHD. Patients in the pivotal trial were 18 to 66 years of age and the BMI ranged from 16 to 40 kg/m^2.[29] Safety and diagnostic performance has not been established in patients with BMI > 40 kg/m^2. Clinical studies established that a maximally stimulated serum growth hormone level of < 2.8 ng/mL (i.e., at the 30, 45, 60, and 90 minute timespoints) after Macrilen administration confirms the presence of adult GHD. Warnings and precautions for Macrilen include QT prolongation, potential for false positive test results with use of strong cytochrome P450 (CYP)3A4 inducers (discontinue and washout strong CYP3A4 inducers before testing), and potential for false negative test results in recent onset hypothalamic disease.

Arginine and levodopa testing have not been systematically evaluated and validated, and because they have a low sensitivity and specificity in adults and transition patients, it is not recommended to utilize these tests

in this population.[53] Additionally, the clonidine, levodopa, and arginine alone tests are generally not recommended because very low growth hormone cutoff points are required to achieve adequate specificity.[27]

Adults with childhood onset GHD may have alterations in body composition, bone mineral density, and lipid metabolism that are alleviated by treatment with somatropin.[15,31] However, some children with a diagnosis of GHD have a normal somatotropic axis when retested in late adolescence.[31,52] Re-evaluation of the somatotropic axis in children diagnosed with GHD is required during the transition period. The transition period is the time from late puberty to establishment of adult muscle and bone composition, and encompasses attainment of adult height.[31] Re-evaluation of the somatotropic axis is most conveniently done when growth has slowed to the point where pediatric somatropin dosing will be discontinued (i.e., the growth velocity is < 2 to 2.5 cm/year. Recommendations for transitional care after childhood somatropin treatment from the Pediatric Endocrine Society guidelines[31] are as follows. Patients with multiple (≥ 3) pituitary hormone deficiencies regardless of etiology, or GHD with a documented causal genetic mutation or specific pituitary/hypothalamic structural defect (except ectopic posterior pituitary) be diagnosed with persistent GHD. These guidelines recommend re-evaluation of the somatotropic axis for persistent GHD in persons with 1) GHD and deficiency of only one additional pituitary hormone, 2) idiopathic isolated GHD, 3) idiopathic isolated GHD with or without a small pituitary/ectopic posterior pituitary, and 4) in patients after irradiation. Testing can be done after a trial of at least 1 month off somatropin treatment. The guidelines also recommend growth hormone provocative testing to evaluate the function of the somatotropic axis in the transition period if indicated by a low IGF-1 level. Persons with idiopathic isolated GHD will very likely test sufficient with GH provocative testing. To continue growth hormone therapy in adulthood, retesting for GHD with GH-stimulation test/s is recommended in most transition patients and at least 1 month after discontinuation of pediatric growth hormone therapy.[53] Retesting is not required in transition patients with evidence of panhypopituitarism (≥ 3 pituitary hormone deficiencies) and low serum IGF-1 levels, patients with genetic defects, and patients with hypothalamic-pituitary structural brain defects.

Adult GHD can be predicted with > 90% accuracy by the presence of three or four pituitary hormone deficiencies in addition to serum IGF-1 concentration that is less than the 2.5th percentile or < -2 SDS.[15,16] This is in the absence of conditions that lower IGF-1. Patients with ≥ 3 pituitary hormone deficiencies and an IGF-1 level below the reference range do not need a growth hormone stimulation test.[16] Because of the nature of the cause of GHD in children with structural lesions with multiple hormone deficiencies and those with proven genetic causes, provocative testing in these adults is not necessary.

Chronic Kidney Disease in Children or Adolescents

Somatropin is indicated for the treatment of growth failure in children with CKD up to the time of kidney transplantation and is effective for increasing the rate of growth.[4] Somatropin therapy has increased final adult height in these patients.[19] An adequate growth response can be assumed if height velocity during the first year of growth hormone treatment is greater than 2 cm per year over basline.[20] This increase is supported by outcomes of controlled-trials specific to patients with chronic kidney disease. In a clinical practice guidelines, for children with CKD, patients who have had a kidney transplant and have persistent growth failure, growth hormone therapy is recommended to be initiated 1 year after transplantation if spontaneous catch-up growth does not occur and steroid-free immunosuppression is not a feasible option.[20]

Noonan Syndrome and Short Stature in Children or Adolescents

Somatropin is indicated for the treatment of children with short stature associated with Noonan syndrome.[3,21] Not all patients with Noonan syndrome have short stature; some will achieve a normal adult height without treatment. The younger the age at start of therapy, the larger the change in height SDS.

Prader-Willi Syndrome

Somatropin is indicated for the treatment of *pediatric* patients who have growth failure due to Prader-Willi syndrome.[1,3,7] Somatropin therapy in children increases linear growth velocity, improves body composition (i.e., decreases the percentage body fat, increases or stabilizes LBM), increases bone mineral density, improves physical strength and agility, and improves final adult height.[22] After final height is attained, there may be potential benefits of somatropin on body composition, peak bone mass, cognition, and quality of life in adults.[22] Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment.[1,3,7]

Short Stature Homeobox-Containing Gene (SHOX) Deficiency in Children or Adolescents
Somatropin is indicated for the treatment of short stature or growth failure in children with SHOX deficiency.[2,6] SHOX deficiency may result from either deletion of one copy of the SHOX gene or from mutation within or outside one copy of the SHOX gene that impairs the production or function of the SHOX protein. Women with Turner syndrome have only a single copy of the SHOX gene because they lack all or part of their second X chromosome.[23] SHOX deficiency is also the primary cause of short stature in most patients with Léri-Weill dyschondrosteosis (syndrome), and SHOX mutations and deletions are found in patients with idiopathic short stature. In one study consisting of a 2-year control period and a subsequent extension period to final height, short prepubertal patients with SHOX deficiency received somatropin.[24]

Children Born Small for Gestational Age

Somatropin is indicated for the treatment of growth failure in children born SGA who fail to exhibit catch-up growth by age 2[1,7] to 4 years.[2,3,6] SGA is defined as a birth weight and/or birth length that is greater than 2 SD (about the 3rd percentile) below mean normal values after adjusting for gestational age and sex. The terms SGA and intrauterine growth restriction (retardation) [IUGR] are used interchangeably in this document. In clinical trials, patients born SGA (including children with Silver-Russell syndrome) without catch-up growth who were 2 to 11 years of age had significant increases in growth when treated with somatropin before puberty.[1,3] Optimal duration of therapy once catch-up growth has been attained is not known.

Almost all patients with Silver-Russell syndrome are born SGA, and postnatal catch-up growth does not occur in the majority of children.[44] An expert consensus statement recommends that patients with Silver-Russell syndrome receive treatment with somatropin as soon as possible.[44] Starting therapy at age 2 to 4 years is adequate for the majority of patients. In some cases, somatropin therapy is started in patients less than 2 years of age who have severe fasting hypoglycemia, severe malnutrition, or severe muscular hypotonia. These experts recommend that somatropin therapy be stopped when height velocity is < 2 cm per year over a 6-month period and when bone age is > 14 years in females or > 17 years in males.

Turner Syndrome
Somatropin is indicated for the treatment of short stature associated with Turner syndrome.[1-4,6,7,25,63]

Short Bowel Syndrome
Somatropin is indicated for the treatment of SBS in adults receiving specialized nutritional support.[11]

Human Immunodeficiency Virus-Associated Wasting or Cachexia
Somatropin is indicated for the treatment of HIV-infected adults with wasting (loss of lean body mass [LBM]) or cachexia to increase LBM and body weight, and improve physical endurance.[9] Somatropin therapy increases LBM, decreases fat mass, and increases physical function in patients with HIV-associated wasting. Studies directly comparing somatropin with other therapies (megestrol, oxandrolone, testosterone, and progressive resistance training) for wasting or cachexia in HIV-infection are lacking.[26]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of somatropin. All reviews will be directed to a clinician (i.e., pharmacist) for verification of criteria. All approvals are provided for 1 year in duration unless otherwise noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with somatropin as well as the monitoring required for adverse events and long-term efficacy, initial approval requires somatropin to be prescribed by or in consultation with a physician who specializes in the condition being treated. Human growth hormone is FDA-approved for treatment of a limited number of conditions. The FDA has not approved the use of human growth hormone as therapy for anti-aging, longevity, cosmetic or performance enhancement. Federal law prohibits the dispensing of human growth hormone for non-approved purposes. A pharmacy's failure to comply with that law could result in significant criminal penalties to the pharmacy and its employees. Accordingly, a pharmacy may decline to dispense prescriptions for human growth hormone when written by physicians or other authorized prescribers who they believe may be involved in or affiliated with the fields of anti-aging, longevity, rejuvenation, cosmetic, performance enhancement or sports medicine.

Documentation: Documentation is required for use of somatropinas noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information. For patient cases in which documentation is required, if this documentation has been previously received upon a prior coverage review, the documentation requirement is considered to be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Genotropin, Humatrope, Norditropin, Nutropin AQ, Omnitrope, Saizen, and Zomacton (all listed products except Serostim and Zorbtive) is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Growth Hormone Deficiency (GHD) in Children or Adolescents.** Approve for *initial* for 1 year therapy in patients who meet the following criteria (A, B, C, D, or E):
   - **A)** Patient meets the following (i or ii and iii):
     - **i.** Patient has had two growth hormone (GH) stimulation tests performed with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon AND both tests show an inadequate response as defined by a peak GH response which is below the normal reference range as determined by the testing laboratory; OR
     - **ii.** Patient meets both of the following criteria (a and b):
       - **a)** Patient has had at least one growth hormone stimulation test performed with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon AND the test shows an inadequate response as defined by a peak GH response which is below the normal reference range as determined by the testing laboratory; AND
       - **b)** Patient has at least one risk factor for growth hormone deficiency (for example, the height for age curve has deviated downward across two major height percentiles [e.g., from above the 25th percentile to below the 10th percentile]; the child's growth rate is less than the expected normal growth rate based on age and gender; low IGF-1 and/or IGFBP-3 levels; the child has a very low peak growth hormone level on provocative testing as defined by the prescribing physician; the child's growth velocity is less than the 10th percentile for age and gender [height velocity percentile is NOT the same as height-for-age percentile]; the

patient is status post craniopharyngioma resection; the patient has optic nerve hypoplasia; the patient has a growth hormone gene deletion); AND

Note: Some children will achieve stimulated growth hormone concentrations in the normal range as determined by the testing laboratory and could be reviewed for authorization under non-GHD short stature (idiopathic short stature).

iii. Patient has been evaluated by an endocrinologist.

B) Patient has *undergone brain radiation or tumor resection* AND meets the following criteria (i and ii):
- **i.** Patient meets at least ONE of the following criteria (a or b):
  - **a)** Patient has had one growth hormone stimulation test with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon AND the test shows an inadequate response as defined by a peak GH response which is below the normal reference range as determined by the testing laboratory; OR
  - **b)** Patient has a deficiency in at least one other pituitary hormone (that is, adrenocorticotropic hormone [ACTH], thyroid-stimulating hormone [TSH], gonadotropin deficiency [luteinizing hormone {LH} and/or follicle stimulating hormone {FSH} deficiency are counted as one deficiency], or prolactin); AND
- **ii.** Patient has been evaluated by an endocrinologist.

C) Patient has *congenital hypopituitarism* AND meets the following criteria (i and ii):
- **i.** Patient meets at least ONE of the following criteria (a or b):
  - **a)** Patient has had one growth hormone stimulation test with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon AND the test shows an inadequate response as defined by a peak GH response which is below the normal reference range as determined by the testing laboratory; OR
  - **b)** Patient has a deficiency in at least one other pituitary hormone (that is, adrenocorticotropic hormone [ACTH], thyroid-stimulating hormone [TSH], gonadotropin deficiency [luteinizing hormone {LH} and/or follicle stimulating hormone {FSH} deficiency are counted as one deficiency], or prolactin) and/or the patient has the imaging triad of ectopic posterior pituitary and pituitary hypoplasia with abnormal pituitary stalk; AND
- **ii.** Patient has been evaluated by an endocrinologist.

D) Patient has *panhypopituitarism* and meets the following criteria (i and ii):
Note: GHD may occur in combination with other pituitary hormone deficiencies and is referred to as hypopituitarism, panhypopituitarism, or multiple pituitary hormone deficiency.

- **i.** Patient meets at least ONE of the following criteria (a, b, or c):
  - **a)** Patient has pituitary stalk agenesis, empty sella, sellar or supra-sellar mass lesion, or ectopic posterior pituitary "bright spot" on magnetic resonance image or computed tomography; OR
  - **b)** Patient has three or more of the following pituitary hormone deficiencies: somatropin (growth hormone), adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), gonadotropin deficiency (luteinizing hormone [LH] and/or follicle stimulating hormone [FSH] deficiency are counted as one deficiency), and prolactin; OR
  - **c)** Patient has had one growth hormone stimulation test with any of the following agents: levodopa, insulin-induced hypoglycemia, arginine, clonidine, or glucagon AND the test

shows an inadequate response as defined by a peak GH response which is below the normal reference range as determined by the testing laboratory; AND

ii. Patient has been evaluated by an endocrinologist.

E) Patient has had a hypophysectomy (surgical removal of pituitary gland).

Children or Adolescents with Growth Hormone Deficiency (GDH) Continuing Somatropin Therapy (i.e., established on somatropin for ≥ 10 months). Approve for 1 year in patients who meet ONE of the following (A, B, or C):

A) *Patients < 12 years of age.* The height has increased by ≥ 2 cm/year in the most recent year.

B) *Adolescents between ≥ 12 years and ≤ 18 years of age.* Patient meets the following criteria (i and ii):

i. Height has increased by ≥ 2 cm/year in the most recent year; AND

ii. The epiphyses are open.

C) *Adolescents or young adults > 18 years of age.* Patient meets the following criteria (i, ii, and iii):

i. Height has increased by ≥ 2 cm/year in the most recent year; AND

ii. The epiphyses are open; AND

iii. Mid-parental height has *not* been attained.

Note: Mid-parental height is the father's height plus the mother's height divided by 2, plus 2.5 inches if male or minus 2.5 inches if female.

Note: Adolescents and young adults with childhood onset GHD who have previously responded to somatropin with increases in height velocity and who have completed linear growth may continue receiving somatropin therapy as a transition adolescent or as an adult. See criteria I.3. (GHD in adults or transition adolescents).

2. Non-Growth Hormone Deficient Short Stature (Idiopathic Short Stature) in Children or Adolescents. Approve 6 months of *initial* therapy if the patient meets the following criteria (A, B, C, D, E, and F).

A) The child is ≥ 5 years of age; AND

B) Patient's baseline height is less than 1.2 percentile or a standard deviation score (SDS) < -2.25 for age and gender; AND

C) Patient's growth (height) velocity is ONE of the following (i or ii):

i. The child is ≥ 5 years of age AND has a growth rate < 4 cm/year; OR

ii. The growth (height) velocity is less than the 10th percentile for age and gender based on at least 6 months of growth data; AND

Note: Height velocity percentile is NOT the same as height for age percentile.

D) Without growth hormone therapy, the patient's predicted adult height is < 160 cm (63 inches) in males or < 150 cm (59 inches) in females; AND

E) The epiphyses are open; AND

F) Patient does not have constitutional delay of growth and puberty (CDGP).

Children or Adolescents with Non-Growth Hormone Deficient Short Stature (Idiopathic Short Stature) Continuing Somatropin Therapy. Approve 1 year of continuation therapy if the patient meets ONE of the following criteria (A, B, C, or D):

A) *Patients ≥ 5 years of age who received somatropin on an initial 6-month trial basis.* The annualized growth rate has doubled in comparison to the previous year. Note: For example, if the growth velocity was 3 cm/year for the year prior to treatment, then the growth velocity must be at least 3 cm in 6 months (baseline velocity was 1.5 cm/6 months) or for example, the growth velocity was

2 cm/year for the year prior to treatment, then after 6 months of somatropin therapy, the growth velocity must be at least 2 cm in 6 months (1 cm/6 months baseline); OR

B) *Patients ≥ 5 years and < 12 years of age* (i.e., established on somatropin for ≥ 10 months). The height has increased by ≥ 2 cm/year in the most recent year; OR

C) *Patients ≥ 12 years of age and ≤ 18 years of age* (i.e., established on somatropin for ≥ 10 months). Patient meets the following criteria (i and ii):

- **i.** Height has increased by ≥ 2 cm/year in the most recent year; AND
- **ii.** The epiphyses are open.

D) *Adolescents and young adults > 18 years of age* (i.e., established on somatropin for ≥ 10 months). Patient meets the following criteria (i, ii, and iii):

- **i.** Height has increased by ≥ 2 cm/year in the most recent year; AND
- **ii.** The epiphyses are open; AND
- **iii.** Mid-parental height has *not* been attained.

  Note: Mid-parental height is the father's height plus the mother's height divided by 2, plus 2.5 inches if male or minus 2.5 inches if female.

3. Growth Hormone Deficiency in Adults or Transition Adolescents. Approve for 1 year in patients who meet the following criteria (A, B, C, and D):

A) The endocrinologist must certify that somatropin is not being prescribed for anti-aging therapy or to enhance athletic ability or for body building; AND

B) Patient must have a diagnosis of GHD that is one of the following (i or ii): [documentation required for all elements]

- **i.** Childhood onset; OR
- **ii.** Adult onset that results from one of the following: growth hormone deficiency (GHD) alone or multiple hormone deficiencies (hypopituitarism) resulting from pituitary disease, hypothalamic disease, pituitary surgery, cranial radiation therapy, tumor treatment, traumatic brain injury, or subarachnoid hemorrhage; AND

C) Patient meets one of the following criteria (i, ii, or iii):

- **i.** Patient (adult or transition adolescent) has known mutations, embryopathic lesions, congenital or genetic defects, or structural hypothalamic-pituitary defects; [documentation required] OR
- **ii.** Patient meets the following criteria (a, b, and c):
  - **a)** Patient (adult onset or transition adolescent) has three or more of the following pituitary hormone deficiencies: Adrenocorticotropic hormone (ACTH), thyroid-stimulation hormone (TSH), gonadotropin deficiency (luteinizing hormone [LH] and/or follicle stimulating hormone (FSH) deficiency are counted as one deficiency), and prolactin [documentation required]; AND
  - **b)** The age and gender adjusted serum insulin-like growth factor-1 (IGF-1) must be below the lower limits of the normal reference range for the reporting laboratory [documentation required]; AND
  - **c)** Other causes of low serum insulin-like growth factor-1 (IGF-1) have been excluded (e.g., malnutrition, prolonged fasting, poorly controlled diabetes mellitus, hypothyroidism, hepatic insufficiency, oral estrogen therapy).

  OR
- **iii.** Patient has had a negative response to one of the following standard growth hormone stimulation tests with the response given for each test and depending on whether an adult or transition adolescent [documentation required];

  Adults: Patient meets ONE of the following criteria (a, b, c, d, e, or f): [documentation required for all elements]

Note: If the patient has had a previous trial of an arginine alone test with a peak response of ≤ 0.4 mcg/L, this would meet the criteria for a negative response to a growth hormone stimulation test.

a) Insulin tolerance test (obtaining at least 3 growth hormone levels in at least a 60 minute timeframe [not including a level at timeframe zero], with adequate hypoglycemia being achieved) with peak response ≤ 5.0 mcg/L; OR

b) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with peak response ≤ 3.0 mcg/L AND the patient's body mass index (BMI) is < 25 kg/m^2; OR

c) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with a peak response ≤ 3.0 mcg/L AND the patient's body mass index (BMI) is ≥ 25 kg/m^2 and ≤ 30 kg/m^2 with, according to the prescriber, a high pretest probability of GH deficiency; OR

d) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with a peak response ≤ 1.0 mcg/L AND the patient's body mass index (BMI) is ≥ 25 kg/m^2 and ≤ 30 kg/m^2 with, according to the prescriber, a low pretest probability of GH deficiency; OR

e) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with peak response ≤ 1.0 mcg/L AND the patient's body mass index (BMI) is > 30 kg/m^2; OR

f) Macrilen™ (macimorelin for oral solution) test (obtaining at least 4 growth hormone levels in at least a 90 minute timeframe [not including a level at timeframe zero]) with peak responses < 2.8 ng/mL (2.8 mcg/L) AND the patient's body mass index (BMI) is ≤ 40 kg/m^2.

Note: The following formula can be used to calculate BMI: BMI equals body weight in kg divided by height meters squared (m^2) [i.e., BMI = kg/m^2].

OR

***Transition Adolescents*:** (The transition period is the time from late puberty to establishment of adult muscle and bone composition, and encompasses attainment of adult height.) The patient meets the following criteria (a and b): [documentation required for all elements]

Note: If the patient has had a trial of a Macrilen test with a peak response of < 2.8 ng/mL (mcg/L), this would meet the criteria for a negative response to a growth hormone stimulation test.

a) Patient has been off somatropin therapy for at least 1 month before retesting with a growth hormone stimulation test; AND

b) Patient meets ONE of the following responses to growth hormone stimulation testing (1, 2, 3, 4, 5 or 6):

(1) Insulin tolerance test (obtaining at least 3 growth hormone levels in at least a 60 minute timeframe [not including a level at timeframe zero], with adequate hypoglycemia being achieved) with peak response ≤ 5.0 mcg/L; OR

(2) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with peak response ≤ 3.0 mcg/L AND the patient's body mass index (BMI) is < 25 kg/m^2; OR

(3) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with a peak response of ≤ 3.0 mcg/L AND the patient's body mass index (BMI) is ≥ 25 kg/m^2 and ≤ 30 kg/m^2 with, according to the prescriber, a high pretest probability of GH deficiency; OR

(4) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with a peak

response ≤ 1.0 mcg/L AND the patient's body mass index (BMI) is ≥ 25 kg/m^2 and ≤ 30 kg/m^2 with, according to the prescriber, a low pretest probability of GH deficiency; OR

(5) Glucagon stimulation test (obtaining at least 3 growth hormone levels in at least 180 minute timeframe [not including a level at timeframe zero]) with peak response ≤ 1.0 mcg/L AND the patient's body mass index (BMI) is > 30 kg/m^2; OR

(6) If both the insulin tolerance test AND glucagon stimulation test are contraindicated, the arginine alone test can be used (obtaining at least 3 growth hormone levels in at least 120 minute timeframe [not including a level at timeframe zero]) with a peak response ≤ 0.4 mcg/L;AND

D) Patient has been evaluated by an endocrinologist.

4. Chronic Kidney Disease in Children or Adolescents. Approve for *initial* therapy for 1 year for growth failure in children with CKD who meet the following criteria (A and B):

A) Patient has or had chronic kidney disease (CKD) as defined by an abnormal creatinine clearance; AND

B) Patient has been evaluated by an endocrinologist or a nephrologist.

Chronic Kidney Disease in Children or Adolescents Continuing Somatropin Therapy (i.e., established on somatropin for ≥ 10 months)**.** Approve for 1 year in patients who meet the following criteria (A and B):

A) Height has increased by ≥ 2 cm/year in the most recent year; AND

B) The epiphyses are open.

5. Noonan Syndrome in Children or Adolescents. Approve for *initial* therapy for 1 year in patients who meet the following criteria (A and B):

A) Patient's baseline height is less than the 5th percentile using a growth chart for children without Noonan syndrome; AND

B) Patient has been evaluated by an endocrinologist.

Noonan Syndrome in Children or Adolescents Continuing Somatropin Therapy (i.e., established on somatropin for ≥ 10 months). Approve for 1 year in patients who meet the following criteria (A and B):

A) Height has increased by ≥ 2 cm/year in the most recent year; AND

B) The epiphyses are open.

6. Prader-Willi Syndrome. Approve for *initial* therapy for 1 year in patients (children or adults) who have been evaluated by an endocrinologist.

Prader-Willi Syndrome in Patients Continuing Somatropin Therapy (i.e., established on somatropin for ≥ 10 months). Approve for 1 year in patients who meet ONE of the following criteria (A or B):

A) *Children and adolescents.* The patient meets the following criteria (i and ii):

i. Height has increased by ≥ 2 cm/year in the most recent year; AND

ii. The epiphyses are open.

Note: When the epiphyses are closed and/or the height velocity is < 2 cm/year, the patient can be reviewed for continuation of therapy as an adult with Prader-Willi syndrome.

B) *Adults or adolescents whose epiphyses are closed and/or whose height velocity is < 2 cm/year* The patient meets the following criteria (i and ii):

i. This physician must certify that somatropin is not being used for anti-aging therapy or to enhance athletic performance/body building; AND

ii. Patient must be evaluated by an endocrinologist or in consultation with an endocrinologist.

7. **Short Stature Homeobox-Containing Gene Deficiency in Children or Adolescents.** Approve for *initial* therapy for 1 year in patients who meet the following criteria (A, B, C, and D):
   A) Patient has short stature homeobox-containing gene (SHOX) deficiency demonstrated by chromosome analysis; AND
   B) Epiphyses are open; AND
   C) Patient's baseline height is less than the 3rd percentile for age and gender; AND
   D) Patient has been evaluated by an endocrinologist.

   Short Stature Homeobox-Containing Gene Deficiency in Children or Adolescents Continuing Somatropin Therapy (i.e., established on somatropin for ≥ 10 months). Approve for 1 year in patients who meet the following criteria (A and B):
   A) Height has increased by ≥ 2 cm/year in the most recent year; AND
   B) The epiphyses are open.

8. **Children Born Small for Gestational Age or with Intrauterine Growth Restriction (Retardation) Including Those with Silver-Russell Syndrome.** Approve for *initial* therapy for 1 year in patients who meet the following criteria (A, B, C, and D):
   A) Patient is ≥ 2 years of age; AND
   B) Patient was born small for gestational age (SGA), which is defined as birth weight and/or birth length that is > 2 standard deviations (SD) below the mean (< -2 SD) for gestational age and gender, and the patient did not have sufficient catch-up growth before age 2 to 4 years; AND
   C) Patient's baseline height is less than the 5th percentile for age and gender; AND
   D) Patient has been evaluated by an endocrinologist.

   Children Born Small for Gestational Age or with Intrauterine Growth Restriction (Retardation) Including Those with Silver-Russell Syndrome Continuing Somatropin Therapy (i.e., established on somatropin for ≥ 10 months). Approve for 1 year in patients who meet ONE of the following (A, B, or C):
   A) *Patients < 12 years of age.* Height has increased by ≥ 2 cm/year in the most recent year.
   B) *Patients ≥ 12 years and ≤ 18 years of age.* The patient meets the following criteria (i and ii):
      i. Height has increased by ≥ 2 cm/year in the most recent year; AND
      ii. The epiphyses are open.
   C) *Adolescents and young adults > 18 years of age.* The patient meets the following criteria (i, ii, and iii):
      i. Height has increased by ≥ 2 cm/year in the most recent year; AND
      ii. Epiphyses are open; AND
      iii. Mid-parental height has *not* been attained.
      Note: Mid-parental height is the father's height plus the mother's height divided by 2, plus 2.5 inches if male or minus 2.5 inches if female.

9. **Turner Syndrome**. Approve for *initial* therapy for 1 year in patients with short stature associated with Turner syndrome.

Patients with Turner Syndrome Continuing Somatropin Therapy (i.e., established on somatropin for ≥ 10 months). Approve for 1 year in patients who meet the following criteria (A and B):
A) Height has increased by ≥ 2 cm/year in the most recent year; AND
B) The epiphyses are open.

II. Coverage of Genotropin, Humatrope, Norditropin, Nutropin AQ, Omnitrope, Saizen, Zomacton, and Zorbtive (all listed products except Serostim) is recommended in patients who meet the following criteria:

1. Short Bowel Syndrome in Adults. Approve of *initial* therapy for 1 month if the patient meets the following criteria (A and B):
A) Patient is ≥ 18 years of age; AND
B) Patient is receiving specialized nutritional support (defined as a high carbohydrate, low-fat diet that is adjusted for individual patient requirements and preferences).

Short Bowel Syndrome in Adults Continuing Somatropin Therapy. Approve a second 1-month course of somatropin if the adult patient responded to somatropin therapy with a decrease in the requirement for specialized nutritional support according to the prescriber.

III. Coverage of Serostim is recommended in those who meet the following criteria:

1. Human Immunodeficiency Virus (HIV) Infection with Wasting or Cachexia in Adults. Approve for 6 months in patients who meet ALL of the following criteria (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) Patient has ONE of the following (i, ii, or iii):
i. Documented unintentional weight loss of ≥ 10% from baseline; OR
ii. Weight < 90% of the lower limit of ideal body weight; OR
iii. Body mass index (BMI) ≤ 20 kg/m^2; AND
Note: The following formula can be used to calculate BMI: BMI equals body weight in kg divided by height in meters squared (m^2) [i.e., BMI = kg/m^2];
C) Patient has wasting or cachexia that is due to malabsorption, poor diet, opportunistic infection, or depression, and other causes have been addressed prior to starting somatropin; AND
D) Patient has been on antiretroviral therapy or highly active antiretroviral treatment (HAART) for ≥ 30 days prior to beginning Serostim therapy and will continue antiretroviral therapy throughout the course of Serostim treatment; AND
E) Serostim is not being used solely for treatment of alterations in body fat distribution such as increased abdominal girth, lipodystrophy and excess abdominal fat, or buffalo hump.

HIV Infection with Wasting or Cachexia in Adults Continuing Serostim Therapy. Approve up to a 6-month course of Serostim if the patient meets the following criteria (A and B):
A) Patient has been off Serostim for at least 1 month; AND
B) Patient meets criteria III.1.A, B, C, D, and E above.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Genotropin, Humatrope, Norditropin, Nutropin AQ, Omnitrope, Saizen, Serostim, and Zorbtive is not recommended in the following situations:
Note: For some of the following indications, authorization for coverage is not recommended because this indication is excluded from coverage in a typical pharmacy benefit.

1. **Acute Critical Illness Due to Complications Following Surgery, Multiple Accidental Trauma, or with Acute Respiratory Failure.**[1-9] In two placebo-controlled trials, in non-growth hormone deficient adults (n = 522) with these conditions, there was a significant increase in mortality (42% vs. 19%) in patients treated with somatropin compared to those on placebo.

2. **Aging (i.e., Antiaging); To Improve Functional Status in Elderly Patients; and Somatopause.**[17,18,32,33] Somatropin is not FDA-approved for anti-aging therapy, to improve functional status in elderly patients, or to treat somatopause. Federal law prohibits the distribution or dispensing of somatropin for non-FDA approved uses. There are no long-term studies assessing somatropin efficacy and safety for anti-aging therapy. Short-term therapy with somatropin may improve some measures of body composition, including increased muscle mass, reduced total body fat, improved skin elasticity, and reduced rate of bone demineralization, but does not have positive effects on strength, functional capacity, or metabolism. Somatropin is associated with considerable adverse effects in non-growth hormone deficient adults (e.g., carpal tunnel syndrome, soft tissue edema, arthralgias, glucose intolerance, increased serum lipids). Another concern is the possible increased risk of cancer with long-term use of somatropin and the potentiating effects of IGFs on cancer. Somatropin is not indicated for the age-related decrease in growth hormone/IGF-1 status.[16]

3. **Athletic Ability Enhancement.**[18,34] Somatropin is not FDA-approved for athletic performance enhancement or for body building in nonathletes. Federal law prohibits the distribution or dispensing of somatropin for non-FDA approved uses. Short-term administration of somatropin to increase strength and endurance in athletes is no more effective than training alone and somatropin should not be administered to athletes or other persons for the purpose of enhancing athletic ability or improving personal appearance (i.e., to appear leaner and more muscular). Somatropin has been used in supraphysiologic doses alone or in combination with other performance enhancing drugs (PEDs) in users who are not athletes.[34] Use of PEDs has been linked to an increased risk of death and many adverse effects including cardiovascular, psychiatric, metabolic, endocrine, neurologic, infectious, hepatic, renal, and musculoskeletal disorders.

4. **Central Precocious Puberty.** Children with precocious puberty are often treated with gonadotropin releasing hormone (GnRH) agonists (Lupron® [leuprolide acetate injection]) to suppress pituitary gonadal activity, to slow the advancement of bone age (prevent premature fusion of the epiphyseal growth plates), and to improve adult height. In some patients GnRH agonist therapy may result in marked deceleration of bone growth and may result in adult height that is less than the midparental height. Somatropin has been used in girls when growth velocity decreases or if it appears that the targeted adult height will not be attained.[35] There are no large well-controlled trials on the efficacy and safety of adding somatropin to GnRH agonist therapy in these children or the effect on final height.[35,36]

5. **Chronic Fatigue Syndrome.** There is no evidence of GHD in chronic fatigue syndrome.[37]

6. **Congenital Adrenal Hyperplasia (CAH).**[38,39] The Endocrine Society clinical practice guidelines on CAH due to steroid 21-hydroxylase deficiency recommends against the use of experimental treatment approaches outside of formally approved clinical trials.[39] Children with predicted adult height SD $\leq$ -2.25 may be considered for growth-promoting treatments in appropriately controlled trials.

7. **Constitutional Delay of Growth and Puberty (CDGP).** These children have delayed skeletal maturation and pubertal development. Administering somatropin does not increase adult height (which is usually normal).[40] Short-term androgen therapy accelerates growth and the rate of pubertal advancement in boys.

8. **Corticosteroid-Induced Short Stature.**[13] This includes a variety of chronic glucocorticoid-dependent conditions, such as asthma, Crohn's disease,[13] juvenile rheumatoid arthritis,[28,41,42] as well as after renal, heart, liver, or bone marrow transplantation.[43] Short-term improvement in growth velocity in children with glucocorticoid-induced suppression has been reported with somatropin therapy. Long-term data are not available.[13] Children being considered for treatment with somatropin should be enrolled in studies that allow careful monitoring and data analysis.

9. **Fibromyalgia.** In one placebo-controlled study, 120 non-GHD adult women with severe fibromyalgia and low levels of IGF-1 were randomized to somatropin 0.006 mg/kg/day for 12 months (dose was adjusted) or placebo for 6 months.[45] Patients receiving placebo initially were switched to somatropin from Months 6 to 12 (open label). Standard therapy for fibromyalgia was continued. After 6 months, there were no differences between somatropin and placebo in the percentage of patients with fewer than 11 positive tender points, mean number of tender points, intensity of pain in every point evaluated, and other measures. After 12 months of somatropin therapy, 53% of patients had less than 11 positive tender points compared with 33% of patients who received placebo and then somatropin for 6 months ($P < 0.05$). At 18 months follow-up evaluation when somatropin was discontinued, impairment in pain perception worsened in both groups but to a lesser extent in the patients on somatropin for 12 months. Further controlled trials are needed with a longer duration,[46] with different doses, and using the 2010 American College of Rheumatology criteria for fibromyalgia. Some patients with fibromyalgia may have adult GHD.

10. **Human Immunodeficiency Virus (HIV)-Infected Patients with Alterations in Body Fat Distribution** (e.g., increased abdominal girth, lipodystrophy and excess abdominal fat, buffalo hump).[26] Somatropin is not indicated for the treatment of HIV-associated adipose redistribution syndrome (HARS). HARS is a subset of HIV lipodystrophy and is defined as maldistribution of body fat characterized by central fat accumulation (lipohypertrophy) with or without lipoatrophy. In HARS, fat may also accumulate in the upper body subcutaneous area such as the dorsocervical area (buffalo hump). These changes may be associated with metabolic disturbances (insulin resistance, glucose intolerance, dyslipidemia) and belly image distress. Safety and efficacy are not established.

11. **Infertility.**[47,10] Clinical trials indicate that somatropin is not useful as an adjunct during in vitro fertilization, for induction of ovulation in polycystic ovary syndrome, or for assisted reproductive technology. The authors of a recent meta-analysis concluded there is no evidence of an increased chance of a live birth with use of somatropin.

12. **Obesity.**[48,49] Somatropin is not indicated for the treatment of obesity. Low growth hormone levels are a consequence of central obesity and not a cause. Obesity is associated with decreased basal and pusatile release of growth hormone and decreased stimulated growth hormone release. Somatropin therapy does not have significant beneficial effects on obesity in persons without GHD and does not produce significant overall weight loss. Supraphysiologic doses of somatropin have been used to treat obesity. Effects of long-term therapy with somatropin are unknown.

13. **Osteoporosis.**[50,51] Guidelines for treatment or prevention of osteoporosis do not include recommendations for use of somatropin. In one double-blind trial, 80 postmenopausal women with osteoporosis (56% of patients [n = 45/80] had a history of fractures) were randomized to somatropin 0.33 mg/day or 0.83 mg/day or to placebo for three years.[50] The double-blind phase was 18 months and patients on somatropin continued drug for another 18 months and patients on placebo stopped at 18 months. Patients were compared with an age-matched random population sample of women (n = 120). All patients received calcium 750 mg, vitamin D 400 units, and hormone replacement therapy. All women were followed for 10 years total. Bone mineral density increased in the patients receiving somatropin at years 4 and 5, and after 10 years, had decreased to similar levels as before treatment. At

10 years, 28% of women (n = 22/80) had had fractures. In the control group, fractures increased from 8% of patients at baseline to 32% of patients after 10 years. At 10 years, 41% of patients (n = 33/80) had stopped hormone replacement therapy; 23% had started bisphosphonates due to fractures, and 3% had received Forteo® (teriparatide injection). Larger studies are needed to determine the effects of somatropin therapy on bone mineral density and fractures in non-growth hormone deficient persons.

14. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	• Removal of Nutropin (obsolete since 2013)	01/16/2019
Selected Revision	• Growth Hormone Deficiency in Children or Adolescents: Criterion related to growth rate and growth velocity percentile were removed. A confirmation of two growth hormone stimulation tests OR one growth hormone stimulation test and a risk factor for growth hormone deficiency was added. Criteria was removed which specified the result of a growth hormone stimulation test was < 10 ng/mL. Criteria was added that the stimulation test show an inadequate response as defined by a peak response below the normal reference range as determined by the testing laboratory. Tumor resection was added to the brain radiation criteria. • Growth Hormone Deficiency in Adults or Transition Adolescents: Growth hormone stimulation tests were updated to include a minimum number of accepted growth hormone values in a specified timeframe required for each test. Criteria was updated for the insulin tolerance test to include information about achieving adequate hypoglycemia. Criterion related to continuation of therapy for Adults and Transition Adolescents were removed. The documentation section of the policy statement was updated to reflect that if documentation had been received upon a prior coverage review, the documentation requirement would be considered met.	05/08/2019
Annual Revision	• Non-Growth Hormone Deficient Short Stature (Idiopathic Short Stature) – clarified criterion ii. as growth (height) velocity. A note was added that height velocity percentile is not the same as height for age percentile. • Growth Hormone Deficiency in Adults or Transition Adolescents – o Criterion "The patient (adult or transition adolescent) had childhood onset growth hormone deficiency (GHD) and has known mutations, embryopathic lesions, congenital defects, or irreversible structural hypothalamic-pituitary lesions/damage" was updated to "The patient (adult or transition adolescent) has known mutations, embryopathic lesions, congenital or genetic defects, or structural hypothalamic-pituitary defects," o Glucagon stimulation test peak response levels were updated for adults and transition adolescents. Peak response levels reflect the patient's body mass index (BMI) and/or pretest probability of growth hormone deficiency. A second test is no longer required for transition adolescents with a BMI of ≥ 25 mg/m2. o Arginine alone stimulation test was removed as a choice for a required stimulation test for adults. A note was added that a previous trial of an arginine alone test with a peak response of ≤ 0.4 mcg/L would meet the criteria for a negative response to a growth hormone stimulation test. o A note was added for transition adolescents that if the patient has had a trial of a Macrilen test with a peak response of < 2.8 ng/mL (mcg/L), this would meet the criteria for a negative response to a growth hormone stimulation test. • Chronic Kidney Disease in Children or Adolescents – Criterion "Patient has chronic kidney disease (CKD) as defined by an abnormal creatinine clearance" was updated to "Patient has or had chronic kidney disease (CKD) as defined by an abnormal creatinine clearance." Continuation criteria were updated to a height increase of ≥ 2 cm/year in the most recent year. • Short Bowel Syndrome in Adults – prescribing physician was replaced by prescriber. • Removal of the following Conditions Not Recommended for Approval: Bony dysplasias (Achondroplasia, Hypochondroplasia), Burn Injury (Extensive) in Children or Adults, Cardiac Transplantation, Crohn's Disease,	2/5/2020

	Cystic Fibrosis, Dilated Cardiomyopathy and Heart Failure, Down's Syndrome, End-Stage Renal Disease in Adults Undergoing Hemodialysis, Familial Dysautonomia (Riley Day Syndrome, Hereditary Sensory Autonomic Neuropathy), Hematopoietic Stem Cell Transplant Without Total Body Irradiation or Cranial Radiation, Kidney Transplant Patients (Children) with a Functional Renal Allograft, Liver Transplantation, Multiple System Atrophy (MSA), Myelomeningocele, Osteogenesis Imperfecta, Thalassemia, X-linked Hypophosphatemic Rickets (Familial Hypophosphatemia, Hypophosphatemic Rickets).	
Selected Revision	• Updated policy statement to direct reviews to a clinician (i.e., pharmacist) for verification of criteria.	4/08/2020
Annual Revision	• Children or Adolescents with Growth Hormone Deficiency (GDH) Continuing Somatropin Therapy; Children or Adolescents with Non-Growth Hormone Deficient Short Stature (Idiopathic Short Stature) Continuing Somatropin Therapy; Children Born Small for Gestational Age or with Intrauterine Growth Restriction (Retardation) Including Those with Silver-Russell Syndrome Continuing Somatropin Therapy: In places the height increase required was 4 cm/year was updated to 2 cm/year. • Noonan Syndrome in Children or Adolescents Continuing Somatropin Therapy; Prader-Willi Syndrome in Patients Continuing Somatropin Therapy; Short Stature Homeobox-Containing Gene Deficiency in Children or Adolescents Continuing Somatropin Therapy; Patients with Turner Syndrome Continuing Somatropin Therapy: In places the height increase was 2.5 cm/year was updated to 2 cm/year.	2/10/2021

PRIOR AUTHORIZATION POLICY

POLICY: Growth Disorders – Increlex Prior Authorization Policy

- Increlex® (mecasermin [rDNA origin] for subcutaneous injection – Ipsen Biopharmaceuticals/Hospira)

REVIEW DATE: 10/14/2020

OVERVIEW

Increlex, an insulin-like growth factor (IGF-1), is indicated for the treatment of growth failure in pediatric patients ≥ 2 years of age with the following conditions:[1]

- **Primary IGF-1 deficiency**, for patients with severe disease, defined as:
  - Height standard deviation score ≤ -3.0; AND
  - Basal IGF-1 standard deviation score ≤ -3.0; AND
  - Normal or elevated growth hormone level.
- **Growth hormone gene deletion**, in patients who have developed neutralizing antibodies to growth hormone.

Increlex is given by subcutaneous injection twice daily, shortly before or after a meal or snack. Treatment with Increlex should continue until the epiphyses fuse indicating full growth potential has been achieved.[3] It is a limitation of use that Increlex is not a substitute to growth hormone for approved growth hormone indications. Increlex is <u>not</u> indicated in secondary forms of IGF-1 deficiency, such as growth hormone deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory corticosteroids.[1]

Disease Overview

IGF-1 is the principal hormonal mediator of growth hormone action.[3] Under normal circumstances, growth hormone binds to its receptor in the liver and other tissues and stimulates the synthesis/secretion of IGF-1. In target tissues, the Type 1 IGF-1 receptor is activated by IGF-1, leading to intracellular signaling which stimulates multiple processes leading to stature growth. The metabolic actions of IGF-1 are in part directed at stimulating the uptake of glucose, fatty acids, and amino acids so that metabolism supports growing tissues. Primary IGF-1 deficiency is a group of disorders characterized by decreased IGF-1 production with normal or increased growth hormone secretion.[2] Three distinct molecular abnormalities have been identified as causes of primary IGF-1 deficiency: 1) mutations or gene deletions of the GH receptor gene; 2) mutations affecting the post-growth hormone receptor signaling cascade, as observed in a patient homozygous for a point mutation of the gene for signal transducer and activator of transcription (STAT)-5b; and 3) mutations or deletions of the gene for IGF-1. These patients are not growth hormone deficient and do not respond adequately to exogenous growth hormone treatment.[1-2] Once a diagnosis of severe primary IGF-1 deficiency is made, treatment is recommended as soon as possible.[3] Growth rates are highest during the first year of treatment and both first year catch-up growth and long-term outcomes are improved when initiated in younger children.

Clinical Efficacy

The efficacy of Increlex was evaluated in five clinical studies in patients (n = 71) with primary IGF-1 deficiency.[1] In these studies, 11% of the patients (n = 7) had growth hormone gene deletion. Refer to Table 1 for pooled height results from these studies in patients treated for up to 8 years.

Table 1: Annual Height Results by Number of Years Treated with Increlex.[1]

	Pre-Tx	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
Height Velocity (cm/yr)									
n	58	58	48	38	23	21	20	16	13
Mean (SD)	2.8 (1.8)	8.0 (2.2)	5.8 (1.5)	5.5 (1.8)	4.7 (1.6)	4.7 (1.6)	4.8 (1.5)	4.6 (1.5)	4.3 (1.1)
P-value*		<0.0001	<0.0001	<0.0001	0.0045	0.0015	0.0009	0.0897	0.3059
Height SDS									
n	61	61	51	40	24	21	20	16	13
Mean (SD)	-6.7 (1.8)	-5.9 (1.8)	-5.6 (1.8)	-5.4 (1.8)	-5.5 (1.9)	-5.6 (1.8)	-5.4 (1.8)	-5.2 (2.0)	-5.2 (2.0)

Pre-Tx – Pre-treatment; SD – Standard deviation; * P-values for comparison vs. pre-Tx values are computed using paired t-tests; SDS – Standard deviation score.

Most clinical assays used by laboratories in the US report IGF-1 values ± two standard deviations (SD) thereby representing the age-related reference range for the reporting laboratory.[4] Reference ranges for IGF-1 vary among laboratories and are dependent upon patient age, gender, and puberty status. However, some laboratories do not routinely report the SDS for IGF-1.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Increlex. Because of the specialized skills required for evaluation and diagnosis of patients treated with Increlex as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Increlex to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Increlex is recommended in those who meet the following criteria:

FDA-Approved Indications

11. Severe Primary Insulin-Like Growth Factor-1 (IGF-1) Deficiency in a Child. Approve for 1 year if the patient meets ONE of the following conditions (A or B):

A) Initial Therapy or Patient has been on Increlex < 1 Year. Approve for 1 year if the patient meets ALL of the following conditions (i, ii, iii, iv, and v):

- **i.** Patient is ≥ 2 years of age; AND
- **ii.** Height standard deviation score is ≤ -3.0 at baseline; AND
- **iii.** Patient has a basal IGF-1 level below the lower limits of the normal reference range for the reporting laboratory; AND
  Note: Reference ranges for IGF-1 vary among laboratories and are dependent upon age, gender, and puberty status.
- **iv.** Growth hormone concentration is normal or increased at baseline; AND
- **v.** Increlex is prescribed by or in consultation with a pediatric endocrinologist.

B) Patient has been receiving Increlex for ≥ 1 Year. Approve for continuation of therapy if the patient meets the following conditions (i and ii):

- **i.** The patient's height has increased by ≥ 4 cm/year in the most recent year; AND
  Note: Patients are reviewed annually for growth rate.
- **ii.** The epiphyses are open.

12. **Growth Hormone Gene Deletion in a Child who has Developed Neutralizing Antibodies to Growth Hormone.** Approve for 1 year if the patient meets ONE of the following conditions (A or B):
    - **A)** Initial Therapy or Patient has been on Increlex < 1 Year. Patient meets both of the following (i and ii):
        - **i.** Patient is ≥ 2 years of age; AND
        - **ii.** Increlex is prescribed by or in consultation with a pediatric endocrinologist.
    - **B)** Patient has been receiving Increlex for ≥ 1 Year. Approve for continuation of therapy if the patient meets BOTH of the following conditions (i and ii):
        - **i.** The patient's height has increased by ≥ 4 cm/year in the most recent year; AND
          Note: Patients are reviewed annually for growth rate.
        - **ii.** The epiphyses are open.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Increlex is not recommended in the following situations:

1. **Idiopathic Short Stature, Growth Hormone Deficiency.** A Phase II open-label study evaluated somatropin in combination with Increlex in children with short stature associated with IGF-1 deficiency.[6] This study includes prepubertal children with IGF-1 SDS of ≤ -1 for age and gender, height SDS ≤ -2 for age and gender, and GH sufficiency demonstrated by a maximal stimulated GH response of ≥ 10 ng/mL; however, results are not yet available. Somatropin monotherapy is indicated for idiopathic short stature.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Increlex® injection [prescribing information]. Basking Ridge, NJ: Ipsen Biopharmaceuticals/Hospira; December 2019.
2. Rosenfeld RG. The IGF system: new developments relevant to pediatric practice. *Endocr Dev*. 2005;9:1-10.
3. Cohen J, Blethen S, Kuntze J, et al. Managing the child with severe primary insulin-like growth factor-1 deficiency (IGFD): IGFD diagnosis and management. *Drugs R D*. 2014;14(1):25-29.
4. Elmlinger MW, Kühnel W, Weber MM, Ranke MB. Reference ranges for two automated chemiluminescent assays for serum insulin-like growth factor I (IGF-I) and IGF-binding protein 3 (IGFBP-3). *Clin Chem Lab Med*. 2004;42(6):654-664.
5. Rosenbloom AL. Is there a role for recombinant insulin-like growth factor-I in the treatment of idiopathic short stature? *Lancet.* 2006;368:612-616.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No changes to the criteria.	10/10/2018
Annual Revision	No changes to the criteria.	10/16/2019
Update	01/08/2020: No criteria changes. Policy was updated to remove a Note with a non-functioning link to an online tool to assess height standard deviation score.	NA
Annual Revision	**Severe Primary Insulin-Like Growth Factor-1 Deficiency in a Child:** For patients starting therapy or taking Increlex for < 1 year, add criteria that requires that the patient is ≥ 2 years of age. **Growth Hormone Gene Deletion in a Child who has Developed Neutralizing Antibodies to Growth Hormone:** For patients starting therapy or taking Increlex for < 1 year, add criteria that requires that the patient is ≥ 2 years of age.	10/14/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Cablivi Prior Authorization Policy

- Cablivi® (caplacizumab-yhdp for injection, for intravenous or subcutaneous use - Genzyme)

REVIEW DATE: 02/03/2021

Overview

Cablivi, a von Willebrand factor (vWF)-directed antibody fragment, is indicated for the treatment of adult patients with **acquired thrombotic thrombocytopenic purpura** (aTTP), in combination with plasma exchange and immunosuppressive therapy.[1] Cablivi is given once a day during plasma exchange and continued for 30 days after the last plasma exchange session. If, after the initial treatment course, there are signs of persistent underlying disease such as suppressed ADAMTS13 (A Disintegrin And Metalloproteinase with ThromboSpondin-1 motif, member 13) levels, Cablivi therapy may be extended for a maximum of 28 days. Cablivi should be discontinued if the patient experiences more than two recurrences of aTTP while on Cablivi.

Disease Overview

Thrombotic thrombocytopenic purpura (TTP) is a rare but potentially fatal blood disorder.[2-5] TTP may be caused by an inherited severe deficiency of plasma ADAMTS13 activity resulting from mutations; this is referred to as hereditary or congenital TTP. More commonly, TTP is acquired and due to autoantibodies that inhibit plasma ADAMTS13 activity, referred to as immune-mediated TTP (iTTP). Reduced ADAMTS13 activity leads to accumulation of ultra-large vWF multimers in the blood, which bind to platelets and lead to excessive platelet clumping in the microvasculature, resulting in multi-organ failure and death. Cablivi is a nanobody that targets the ultra-large vWF and inhibits the interaction between vWF and platelets, thereby preventing platelet adhesion.[1-3,6]

Guidelines/Recommendations

The standard of care for treatment aTTP is plasma exchange and glucocorticoids.[7] Plasma exchange removes the ultra-large vWF and autoantibodies and replenishes ADAMTS13, and immunosuppressants inhibit autoantibody formation.[2,6,7] Rituximab can also be added to the aTTP treatment regimen.[3] Rituximab has been shown to reduce the incidence of aTTP relapse by diminishing the production of anti-ADAMTS13 antibodies and restoring ADAMTS13 activity.[3,4]

The International Society on Thrombosis and Haemostasis (ISTH) formed a multidisciplinary panel including hematologists and pathologists with clinical expertise in the diagnosis and management of TTP, clinicians from other relevant disciplines, and patient representatives to issue recommendations about treatment of TTP (2020).[8] For patients with aTTP or iTTP experiencing an acute event (first event or relapse), the panel suggests using Cablivi over not using Cablivi. The panel stressed that Cablivi should only be given under the guidance of an experienced clinician; ideally, a TTP expert (e.g., a hematologist or pathologist specialized in transfusion medicine with previous experience in treating the disease).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cablivi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cablivi as well as the monitoring required for adverse events and efficacy, approval requires Cablivi to be prescribed by or in consultation with a physician who specializes in the condition being treated. Note that one course of treatment consists of Cablivi to be administered in conjunction with plasma exchange and Cablivi to be administered for up to 60 days (one dose per day) following the last plasma exchange session.

Automation: None.

Recommended Authorization Criteria

Coverage of Cablivi is recommended in those who meet the following criteria:

FDA-Approved Indications

19. Acquired Thrombotic Thrombocytopenic Purpura (aTTP). Approve for one course of treatment (up to 60 days following the last plasma exchange session) if the patient meets ALL of the following criteria (A, B, C, D, and E):

- **I)** Patient is ≥ 18 years of age; AND
- **J)** Cablivi was initiated in the inpatient setting, in combination with plasma exchange therapy; AND
- **K)** Patient is currently receiving at least one immunosuppressive therapy; AND
  Note: Examples include systemic corticosteroids, rituximab (or a rituximab product), cyclosporine, cyclophosphamide, mycophenolate mofetil, hydroxychloroquine, Velcade® [bortezomib for injection]).
- **L)** If the patient has previously received Cablivi, he/she has not had more than two recurrences of aTTP while on Cablivi; AND
- **M)** The medication is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cablivi is not recommended in the following situations:

9. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Cablivi® for injection [prescribing information]. Cambridge, MA: Genzyme Corporation; September 2020.
2. Duggan S. Caplacizumab: first global approval. *Drugs*. 2018;78:1639-1642.
3. Coppo P, Cuker A, George JN. Thrombotic thrombocytopenic purpura: toward targeted therapy and precision medicine. *Res Pract Thromb Haemost*. 2019;3:26-37.

4. Joly BS, Coppo P, Veyradier A. Thrombotic thrombocytopenic purpura. *Blood.* 2017;129:2836-2846.
5. Zheng XL, Vesely SK, Cataland SR, et al. International Society on Thrombosis and Haemostasis (ISTH) guidelines for the diagnosis of thrombotic thrombocytopenic purpura. *J Thromb Haemost*. 2020;18:2486-2495.
6. Scully M, Cataland SR, Peyvandi F, et al. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. *N Engl J Med*. 2019;380:335-346.
7. Scully M, Hunt BJ, Benjamin S, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. *Br J Haematol*. 2012;158:323-335.
8. Zheng XL, Vesely SK, Cataland SR, et al. International Society on Thrombosis and Haemostasis (ISTH) guidelines for the treatment of thrombotic thrombocytopenic purpura. *J Thromb Haemost*. 2020;18:2496-2502.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	02/20/2019
Selected Revision	Revised criterion "The patient is currently receiving daily plasma exchange and at least one immunosuppressant therapy (e.g., corticosteroids with or without a rituximab product" to "The patient is currently receiving at least one immunosuppressive therapy (e.g., systemic corticosteroids, rituximab [or a rituximab product], cyclosporine [Neoral®, Sandimmune®, generics], cyclophosphamide, mycophenolate mofetil, [CellCept®, Myfortic®, generics], hydroxychloroquine, Velcade® [bortezomib for injection]).	02/27/2019

Annual Revision	The following changes were made:
	• **Policy Statement:** This section was revised from "All approvals are provided for the duration noted below" to "All approvals are provided for one course of therapy. Note that one course of therapy consists of Cablivi to be administered in conjunction with plasma exchange and Cablivi to be administered for a maximum of 60 days (one dose per day) following the last plasma exchange".
	• **Acquired Thrombotic Thrombocytopenic Purpura (aTTP):**
	  • The approval duration was changed from 3 months to "one course of treatment (up to 60 days following the last plasma exchange session).
	  • Two criteria were added: Cablivi was initiated in the inpatient setting in combination with plasma exchange therapy; and If the patient has previously received Cablivi therapy, he/she has not had more than two recurrences of aTTP while on Cablivi therapy.
	  • Examples of immunosuppressant therapies (of which at least one is required to be used in conjunction with Cablivi) were removed from the criteria and changed to a note.
		01/29/2020

Annual Revision	No criteria changes.	02/03/2021

PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Ceprotin Prior Authorization Policy

- Ceprotin® (protein C concentrate [human] injection for intravenous use – Baxalta/Shire)

REVIEW DATE: 10/28/2020

OVERVIEW

Ceprotin is indicated for pediatric and adult patients with **severe congenital protein C deficiency for the prevention and treatment of venous thrombosis and purpura fulminans**.[1]

Disease Overview

Mutations in the *PROC* gene lead to deficiency of protein C, which is a natural anticoagulant.[2] Individuals with heterozygous *PROC* mutation present with milder disease but are at risk for development of venous thromboembolism. The milder form is present in about 1:200 to 1:500 people in the general population. Most individuals with mild protein C deficiency do not require treatment; anticoagulant therapy may be used for individuals with strong family history of venous thromboembolism. Those who have mutations in both *PROC* genes develop severe symptoms within a few hours to days after birth. The prevalence of severe protein C deficiency is approximately 1:500,000 to 1:750,000 in the general population. In severe protein C deficiency, a complication called purpura fulminans may arise in which blood clots form throughout the body. Blood clots affect the extremities most often but can become widespread (disseminated intravascular coagulation), leading to tissue necrosis.

Diagnosis is based on characteristic symptoms and detailed family history, in addition to measurement of protein C activity or antigen levels.[3,4] It is critical to exclude any acquired reason for protein C deficiency, which is more common than congenital protein C deficiency.[3] Potential causes of acquired deficiency include vitamin K antagonists (e.g., warfarin), vitamin K deficiency, chronic liver disease, recent thrombosis, recent surgery, or disseminated

intravascular coagulation. Diagnostic recommendations from the International Society of Thrombosis and Hemostasis recommend waiting until 30 days after vitamin K antagonist treatment ends to perform protein C assay testing.[4] Molecular genetic testing is only available in a few research laboratories and is not routinely used in clinical diagnosis.[3]

Xigris® (drotrecogin alfa [activated]), a recombinant form of human protein C, was previously marketed for the reduction of mortality in adults with severe sepsis; this was voluntarily withdrawn on October 25, 2011 after failure to show survival benefit vs. placebo.[5] Ceprotin is not labeled for use in this setting.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Ceprotin. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ceprotin as well as the monitoring required for adverse events and long-term efficacy, approval requires Ceprotin to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ceprotin is recommended in those who meet one of the following criteria:

FDA-Approved Indications

45. Protein C Deficiency, Severe. Approve for 1 year if the patient meets the following criteria (A, B, C, and D)

- **A)** The diagnosis of protein C deficiency is confirmed by at least one of the following (i, ii, or iii):
  - **i.** Plasma protein C activity below the lower limit of normal based on the age-specific reference range for the reporting laboratory; OR
  - **ii.** Plasma protein C antigen below the lower limit of normal based on the age-specific reference range for the reporting laboratory; OR
  - **iii.** Genetic testing demonstrating biallelic mutations in the *PROC* gene; AND
- **B)** Acquired causes of protein C deficiency have been excluded; AND
  Note: Examples of acquired causes of protein C deficiency include recent use vitamin K antagonists (e.g., warfarin) within 30 days, vitamin K deficiency, chronic liver disease, recent thrombosis, recent surgery, or disseminated intravascular coagulation.
- **C)** According to the prescriber, patient has a current or prior history of symptoms associated with severe protein C deficiency (e.g., purpura fulminans, thromboembolism); AND
- **D)** Ceprotin is being prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ceprotin is not recommended in the following situations:

51. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

138. Ceprotin® injection for intravenous use [prescribing information]. Lexington, MA: Baxalta/Shire; December 2018.
139. Protein C Deficiency. National Organization of Rare Disorders. Updated 2016. Available at: https://rarediseases.org/rare-diseases/protein-c-deficiency/. Accessed on October 2, 2020.
140. Dinarvand P, Moser KA. Protein C deficiency. *Arch Pathol Lab Med*. 2019 Oct;143(10):1281-1285.
141. Cooper PC, Pavlova A, Moore GW, et al. Recommendations for clinical laboratory testing for protein C deficiency, for the subcommittee on plasma coagulation inhibitors of the ISTH. *J Thromb Haemost*. 2020 Feb;18(2):271-277.
142. Lilly announces withdrawal of Xigris® following recent clinical trial results [press release]. Indianapolis, IL: Eli Lilly; October 25, 2011. Available at: https://investor.lilly.com/news-releases/news-release-details/lilly-announces-withdrawal-xigrisr-following-recent-clinical. Accessed on October 2, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/02/2019
Annual Revision	**Protein C Deficiency, Severe:** Criteria were added requiring confirmation of the diagnosis based on protein C activity or antigen levels or based on molecular genetic testing, current or prior history of symptoms associated with severe protein C deficiency (e.g., purpura fulminans, thromboembolism), and exclusion of acquired causes of protein C deficiency.	10/28/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Coagadex Prior Authorization Policy

- Coagadex® (coagulation Factor X [human] injection for intravenous use – BPL)

REVIEW DATE: 09/09/2020

OVERVIEW

Coagadex, a plasma-derived coagulation Factor X product, is indicated for use in adults and children with hereditary Factor X deficiency for:[1]

- **On-demand treatment and control** of bleeding episodes.
- **Perioperative management** of bleeding in patients with mild and moderate hereditary Factor X deficiency.
- **Routine prophylaxis** to reduce the frequency of bleeding episodes.

Disease Overview

Factor X deficiency, a rare autosomal recessive inherited bleeding disorder the affects approximately 1 in 500,000 to 1,000,000 patients worldwide.[2] The Factor X protein has a key role to assist in activating the enzymes that are key in clot formation. In this condition, blood does not clot properly. Patients experience easy bruising, nose or mouth bleeds and bleeding after trauma or surgery. Among patients with severe Factor X deficiency, umbilical cord bleeding can be one of the first signs; however, bleeding may present at any time. Serious bleeds include spontaneous head bleeds, spinal cord bleeds, and gastrointestinal bleeds. Women who have the condition may experience heavy menstrual bleeding or have menorrhagia. During pregnancy, women may miscarry during the first trimester or have other complications during labor and delivery. However, Factor X deficiency has an equal prevalence in men and women. It is recommended to maintain trough levels of around 20% to 30%. Other treatments include fresh frozen plasma, prothrombin complex concentrates, and Coagadex.

Guidelines

The National Hemophilia Foundation Medical and Scientific Advisory Council has guidelines for the treatment of hemophilia and other bleeding disorders (revised February 2020).[3] Coagadex is recommended in patients who have Factor X deficiency.[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Coagadex. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Coagadex as well as the monitoring required for adverse events and long-term efficacy, approval requires Coagadex to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Coagadex is recommended in those who meet the following criteria:

FDA-Approved Indication

34. Hereditary Factor X Deficiency. Approve for 1 year if the agent is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Coagadex is recommended in those who meet the following criteria:

52. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

143. Coagadex® injection for intravenous use [prescribing information]. Plainsboro, NJ: Noro Nordisk; November 2018.
144. Menegatti M, Peyvandi F. Treatment of rare factor deficiencies other than hemophilia. *Blood*. 2019;133(5):415-424.
145. National Hemophilia Foundation. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders (Revised February 2020). MASAC Document #259. Adopted March 16, 2020. Available at: https://www.hemophilia.org/sites/default/files/document/files/259_treatment.pdf. Accessed on September 4, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	09/11/2019
Annual revision	No criteria changes.	09/09/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Corifact Prior Authorization Policy

- Corifact® (Factor XIII Concentrate [human] injection for intravenous use – CSL Behring

REVIEW DATE: 09/09/2020

OVERVIEW

Corifact, a Factor XIII concentrate, is indicated for adult and pediatric patients with congenital Factor XIII deficiency for:[1]

- **Peri-operative management** of surgical bleeding.
- **Routine prophylactic** treatment.

Disease Overview

Congenital Factor XIII deficiency is caused by defects in both Factor XIIIA and Factor XIIIB genes.[2] However, most cases are due to genetic alterations on the Factor XIIIA gene. The estimated prevalence of Factor XIIIA deficiency is one case in 2 million patients. Clinical symptoms include delayed wound healing, bleeding of soft and subcutaneous tissue, recurrent spontaneous miscarriage, and central nervous system (CNS) bleeding, which may be life-threatening. If patients have severe Factor XIII deficiency, early manifestations include bleeding from the umbilical cord or CNS. Prospective data showed that a level of 30% Factor XIII clotting activity is an adequate therapeutic target for most patients. Treatment of Factor XIII deficiency involves use of fresh frozen plasma, cryoprecipitate, Corifact, or Tretten® (coagulation Factor XIIIA-Subunit [recombinant] injection for intravenous use).

Guidelines

The National Hemophilia Foundation Medical and Scientific Advisory Council has guidelines for the treatment of hemophilia and other bleeding disorders (revised February 2020).[3] Corifact is recommended in patients who have Factor XIII deficiency.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Corifact. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Corifact as well as the monitoring required for adverse events and long-term efficacy, approval requires Corifact to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Corifact is recommended in those who meet the following criteria:

FDA-Approved Indication

35. Congenital Factor XIII Deficiency. Approve for 1 year if the agent is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Corifact recommended in those who meet the following criteria:

53. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

146. Corifact® injection for intravenous use [prescribing information]. Kankakee, IL: CSL Behring; December 2019.
147. Menegatti M, Peyvandi F. Treatment of rare factor deficiencies other than hemophilia. *Blood*. 2019;133(5):415-424.
148. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders (Revised February 2020). MASAC Document #259. Adopted on March 16, 2020. Available at: https://www.hemophilia.org/node/3675. Accessed on September 7, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	09/11/2019
Annual revision	No criteria changes.	09/09/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Fibrinogen Products Prior Authorization Policy

- Fibryga® (fibrinogen [human] for intravenous use – Octapharma USA)
- RiaSTAP® (fibrinogen concentrate [human] for intravenous use – CSL Behring)

REVIEW DATE: 10/28/2020; selected revision 01/27/2021

OVERVIEW

Fibryga and RiaSTAP, human fibrinogen concentrates, are indicated for treatment of acute bleeding episodes in patients with **congenital fibrinogen deficiency**, including afibrinogenemia and hypofibrinogenemia.[1,2] Fibryga prescribing information notes that it is not indicated for dysfibrinogenemia.

Both Fibryga and RiaSTAP are indicated for use in adult and pediatric patients.[1,2] Fibryga and RiaSTAP have been compared in a randomized pharmacokinetic study and are not bioequivalent.[3]

Disease Overview

Congenital deficiencies in fibrinogen (also known as Factor I) can be quantitative or qualitative.[4,5] Quantitative disorders include afibrinogenemia (absence of circulating fibrinogen) and hypofibrinogenemia (low levels of circulating fibrinogen). By contrast, dysfibrinogenemia is a qualitative deficiency in which fibrinogen levels are adequate but function is impaired. In all cases, clinical presentation is variable but bleeding and thromboembolism are possible.

Diagnosis is made by routine coagulation tests in addition to fibrinogen assays.[6] An accurate diagnosis is crucial to distinguish between quantitative and qualitative disorders and guide appropriate treatment. Treatment of fibrinogen deficiency is generally on-demand for acute bleeding episodes, although effective prophylaxis has been used in high-

risk patients (e.g., secondary prevention after cerebral hemorrhage, primary prevention during pregnancy to prevent miscarriage).[7,8]

Guidelines

Guidelines are available from the British Committee for Standards in Haemotology (2014); the guideline was written prior to approval of Fibryga.[9] Regarding diagnosis, it is noted that afibrinogenemia and hypofibrinogenemia manifest as prolonged prothrombin time and activated partial thromboplastin time, as well as reduced fibrinogen activity and fibrinogen antigen. Fibrinogen concentrate (e.g., RiaSTAP) may be required to treat or prevent bleeding. Cryoprecipitate is noted to be similarly effective to fibrinogen concentrate but may be associated with transfusion reactions or volume overload.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of fibrinogen products (Fibryga, RiaSTAP). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with fibrinogen products as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Fibryga and RiaSTAP is recommended in those who meet the following criteria:

FDA-Approved Indications

36. Congenital Fibrinogen Deficiency (Factor I Deficiency), Including Afibrinogenemia and Hypofibrinogenemia. Approve for 1 year if the patient meets the following criteria (A and B):

- **A)** The diagnosis is confirmed by the following laboratory testing (i and ii):
  - **i.** Prolonged activated partial thromboplastin time and prothrombin time at baseline, as defined by the laboratory reference values; AND
  - **ii.** Lower than normal plasma functional and antigenic fibrinogen levels at baseline, as defined by the laboratory reference values; AND
- **B)** The requested agent is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Fibryga and RiaSTAP is not recommended in the following situations:

54. Concomitant Use of Fibryga and RiaSTAP. There are no data to support concomitant use of these products.

55. Dysfibrinogenemia. In dysfibrinogenemia, patients have adequate levels of fibrinogen but dysfunctional clotting.[3,4] Prescribing information for Fibryga notes that it is not indicated in dysfibrinogenemia.[2] RiaSTAP should also not be used in these patients due to risk for thromboembolism.[4]

56. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

149. RiaSTAP® for intravenous use [prescribing information]. Kankakee, IL: CSL Behring; July 2020.
150. Fibryga® for intravenous use [prescribing information]. Hoboken, NJ: Octapharma USA; December 2020.

151. Ross C, Rangarajan S, Karimi M, et al. Pharmacokinetics, clot strength and safety of a new fibrinogen concentrate: randomized comparison with active control in congenital fibrinogen deficiency. *J Thromb Haemost*. 2018 Feb;16(2):253-261.
152. De Moerloose P, Casini A, Neerman-Arbez M. Congenital fibrinogen disorders: an update. *Semin Thromb Hemost*. 2013;39(6):585-595. Available at: https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0033-1349222#TB01978-1. Accessed on October 12, 2020.
153. Factor I (Fibrinogen) Deficiency. National Hemophilia Foundation. Available at: https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Other-Factor-Deficiencies/Factor-I. Accessed on October 12, 2020.
154. Casini A, Unda A, Palla R, et al. Diagnosis and classification of congenital fibrinogen disorders: communication from the SSC of the ISTH. *J Thromb Hemost.* 2018;16(9). Available at: https://onlinelibrary.wiley.com/doi/full/10.1111/jth.14216. Accessed on October 12, 2020.
155. Congenital afibrinogenemia. National Organization for Rare Disorders. Updated 2018. Available at: https://rarediseases.org/rare-diseases/afibrinogenemia-congenital/. Accessed on October 12, 2020.
156. Palla R, Peyvandi F, Shapiro AD. Rare bleeding disorders: diagnosis and treatment. *Blood.* 2015;125(13):2052-2061.
157. Mumford AD, Ackroyd S, Alikhan R, et al.; BCSH Committee. Guideline for the diagnosis and management of the rare coagulation disorders: a United Kingdom Haemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology. *Br J Haematol*. 2014 Nov;167(3):304-26.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/02/2019
Annual Revision	**Congenital Fibrinogen Deficiency (Factor I Deficiency), Including Afibrinogenemia and Dysfibrinogenemia:** Added criterion for Fibryga that patients must be ≥ 12 years of age based on product labeling.	10/28/2020
Selected Revision	**Congenital Fibrinogen Deficiency (Factor I Deficiency), Including Afibrinogenemia and Dysfibrinogenemia:** For Fibryga, the criterion that patients must be ≥ 12 years of age was removed, based on updated product labeling.	01/27/2021

PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Reblozyl Prior Authorization Policy

- Reblozyl® (luspatercept-aamt for subcutaneous injection)

REVIEW DATE: 12/02/2020

OVERVIEW

Reblozyl is an erythroid maturation agent indicated for the following conditions:[1]

- **Beta-thalassemia**, for treatment of adults with anemia who require regular red blood cell (RBC) transfusions.
- **Myelodysplastic syndromes** with ring sideroblasts (MDS-RS) or **myelodysplastic/myeloproliferative neoplasm** with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) associated anemia, for those failing an erythropoiesis stimulating agent and requiring two or more RBC units over 8 weeks in adult patients with very low- to intermediate-risk disease.

Safety and efficacy have not been established in patients < 18 years of age.

Disease Overview

Beta-thalassemia, an inherited blood disorder, is characterized by reduced levels of functional hemoglobin.[2] Patients with a severe form (beta-thalassemia major) become symptomatic due to low hemoglobin level (e.g., increased cardiac effort, tachycardia, poor growth) or ineffective erythropoiesis (e.g., bone changes, massive splenomegaly). Even with treatment, severe complications may arise due to iron overload secondary to increased intestinal absorption and frequent blood transfusions. The frequency of symptomatic patients with beta-thalassemia is estimated at approximately 1 in 100,000 individuals in the general population but is less common in the US.

Myelodysplastic syndromes are cancers in which cells in the bone marrow do not mature and become healthy blood cells.[5] Patients with MDS with refractory anemia and ring sideroblasts have too few RBCs in the blood with too much iron inside the cell. However, the number of white blood cells and platelets are normal. Supportive therapy may include transfusions and use of erythropoiesis-stimulating agents (ESAs). ESAs may be given to increase the number of mature RBCs made by the body and to lessen the effects of anemia. Myelodysplastic/myeloproliferative neoplasms are diseases of the blood and bone marrow with features of myelodysplastic syndromes as well as myeloproliferative neoplasms (e.g., a greater than normal number of blood stem cells become one or more types of blood cells and the total number of blood cells slowly increases). In the pivotal study evaluating Reblozyl for MDS/MPN, patients with deletion 5q were excluded from enrollment. All patients were required to have disease refractory to ESAs (unless endogenous erythropoietin level was elevated), and the median pretransfusion hemoglobin level was 7.6 g/dL (range, 5 to 10 g/dL).

Dosing Information

For all indications, the starting dose is 1 mg/kg given subcutaneously once every 3 weeks.[1] Assess and review hemoglobin levels and transfusion record prior to each dose. Discontinue if a patient does not experience a decrease in transfusion burden after 9 weeks of treatment (administration of three doses) at the maximum dose level. For beta

thalassemia, the maximum recommended dose is 1.25 mg/kg given once every 3 weeks. For MDS and MDS/MPN, the maximum dose is 1.75 mg/kg given once every 3 weeks.

Guidelines

Guidelines do not address Reblozyl for treatment of beta-thalassemia. Standards of Care Guidelines for Thalassemia (2012) are published by the Children's Hospital and Research Center of Oakland.[3] Life-long blood transfusions and iron chelation are the main treatments for beta-thalassemia. Transfusions are usually needed every 3 to 4 weeks and are recommended to maintain the pre-transfusion Hb level above 9 to 10 g/dL and post-transfusion Hb level should not exceed 14 g/dL. Blood transfusions are given to improve anemia as well as suppress ineffective erythropoiesis. Most serious growth, bone, and neurologic complications are prevented with regular transfusions. Once transfusions are started, transfusion-related complications become a major source of morbidity. Hydroxyurea is described as an experimental agent for beta-thalassemia. The Thalassaemia International Federation (2014) also recommends transfusions and iron chelation for treatment of beta-thalassemia.[4] These guidelines state that transfusions are usually administered every 2 to 5 weeks and are recommended to maintain the pre-transfusion Hb level above 9 to 10.5 g/dL and post-transfusion Hb level below 14 to 15 g/dL. The primary goal of chelation therapy is to maintain safe levels of body iron by balancing iron from blood transfusion with iron excretion by chelation. Despite literature suggesting hydroxyurea may be beneficial in certain patients with beta-thalassemia, use is not recommended outside of a clinical trial.

The National Comprehensive Cancer Network (NCCN) guidelines for MDS (version 1.2021 – September 11, 2020) recommend Reblozyl in patients symptomatic anemia due to MDS, in patients without del(5q), who have no response to ESAs (defined by rise in hemoglobin level or decrease in transfusion burden) following 3 to 4 months of treatment.[6] Reblozyl is also a treatment option for patients who have serum erythropoietin levels > 500 mU/mL. Reblozyl is also a treatment option for MDS/MPN with ring sidroblasts and thrombocytosis.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Reblozyl. All approvals are provided for the duration noted below. In cases where the authorization is provided in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Reblozyl as well as the monitoring required for adverse events and long-term efficacy, approval requires Reblozyl to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Reblozyl is recommended in those who meet the following criteria:

FDA-Approved Indications

37. Beta-Thalassemia. Approve for the duration noted if the patient meets one of the following criteria (A or B):
- **A)** Initial Therapy. Approve for 4 months if the patient meets all of the following (i, ii, and iii):
  - **i.** Patient is ≥ 18 years of age; AND
  - **ii.** According to the prescriber, the patient requires regular red blood cell transfusions. Note: This includes patients who are transfusion-dependent; AND
  - **iii.** The medication is being prescribed by or in consultation with a hematologist.
- **B)** Patient is Currently Receiving Reblozyl. Approve for 1 year if, according to the prescriber, the patient has experienced a clinically meaningful decrease in transfusion burden.

38. Myelodysplastic Syndrome. Approve for the duration noted if the patient meets one of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, vi, vii, viii, and ix):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** According to the prescriber, the patient has myelodysplastic syndromes with ring sideroblasts; AND
- **iii.** Patient has very low- to intermediate-risk myelodysplastic syndromes, as determined by the prescriber; AND
  Note: This is determined using the International Prognostic Scoring System (IPSS).
- **iv.** Patient does not have a confirmed mutation with deletion 5q (del 5q); AND
- **v.** Patient currently requires blood transfusions, defined as at least two red blood cell units over the previous 8 weeks; AND
- **vi.** Patient meets ONE of the following (a or b):
  - **a)** Patient tried an erythropoiesis stimulating agent for at least 3 months, unless intolerant; OR
  - **b)** Serum erythropoietin level is greater than 500 mU/L; AND
- **vii.** Pretreatment hemoglobin level is < 10.0 g/dL; AND
- **viii.** Reblozyl will not be used in combination with an erythropoiesis stimulating agent; AND
- **ix.** The medication is being prescribed by or in consultation with an oncologist or hematologist.

B) Patient is Currently Receiving Reblozyl. Approve for 1 year if, according to the prescriber, the patient has experienced a clinically meaningful decrease in transfusion burden.

39. Myelodysplastic/Myeloproliferative Neoplasm. Approve for the duration noted if the patient meets one of the following criteria (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets all of the following criteria (i, ii, iii, iv, v, vi, vii, viii, and ix):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** According to the prescriber, the patient has myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis-associated anemia; AND
- **iii.** Patient has very low- to intermediate-risk disease, as determined by the prescriber; AND
  Note: This is determined using the International Prognostic Scoring System (IPSS).
- **iv.** Patient does not have a confirmed mutation with deletion 5q (del 5q); AND
- **v.** Patient currently requires blood transfusions, defined as at least two red blood cell units over the previous 8 weeks; AND
- **vi.** Patient meets ONE of the following (a or b):
  - **a)** Patient tried an erythropoiesis stimulating agent for at least 3 months, unless intolerant; OR
  - **b)** Serum erythropoietin level is greater than 500 mU/L; AND
- **vii.** Pretreatment hemoglobin level is < 10.0 g/dL; AND
- **viii.** Reblozyl will not be used in combination with an erythropoiesis stimulating agent; AND
- **ix.** The medication is being prescribed by or in consultation with an oncologist or hematologist.

B) Patient is Currently Receiving Reblozyl. Approve for 1 year if, according to the prescriber, the patient has experienced a clinically meaningful decrease in transfusion burden.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Reblozyl is not recommended in the following situations:

57. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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159. National Organization for Rare Disorders (NORD). Beta thalassemia. Available at: https://rarediseases.org/rare-diseases/thalassemia-major//. Accessed on November 17, 2020.
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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	11/13/2019
Update	11/18/2019: No criteria changes. Note added to clarify that the requirement for regular blood cell transfusions includes patients who are transfusion-dependent.	--
Update	12/17/2019: No criteria changes. Dosing added to the overview to support initial approval duration of 4 months. Labeling supports discontinuation of Reblozyl if benefit not observed after 6 weeks at starting dose followed by 9 weeks at the maximum dose.	--
Selected Revision	**Myelodysplastic Syndromes and Myelodysplastic/Myeloproliferative Neoplasm:** These new FDA-approved indications were added to the policy.	04/15/2020
Annual Revision	No criteria changes.	12/02/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Tretten Prior Authorization Policy

- Tretten® (coagulation Factor XIII A-Subunit [recombinant] injection for intravenous use – NovoNordisk)

REVIEW DATE: 09/09/2020

OVERVIEW

Tretten, a coagulation Factor XIII A-Subunit, is indicated for routine prophylaxis of bleeding in patients with congenital factor XIII A-subunit deficiency.[1] The agent is not for use in patients with congenital Factor XIII B-subunit deficiency.

Disease Overview

Congenital Factor XIII deficiency is caused by defects in both Factor XIIIA and Factor XIIIB genes.[2] However, most cases are due to genetic alterations on the Factor XIIIA gene. The estimated prevalence of Factor XIIIA deficiency is one case in 1 to 2 million people. Clinical symptoms include delayed wound healing, bleeding of soft and subcutaneous tissue, recurrent spontaneous miscarriage, and central nervous system (CNS) bleeding, which may be life-threatening. If patients have severe Factor XIII deficiency, early manifestations include bleeding from the umbilical cord or CNS. Prospective data showed that a level of 30% Factor XIII clotting activity is an adequate therapeutic target for most patients. Treatment of Factor XIII deficiency involves use of fresh frozen plasma, cryoprecipitate, Corifact® (Factor XIII concentration injection for intravenous use), or Tretten.

Guidelines

The National Hemophilia Foundation Medical and Scientific Advisory Council has guidelines for the treatment of hemophilia and other bleeding disorders (revised February 2020).[3] Tretten is recommended in patients who have

factor XIII deficiency who lack the factor XIII-A subunit. It will not work in patients who only lack factor XIII-B subunit.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Tretten. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tretten as well as the monitoring required for adverse events and long-term efficacy, Tretten approval requires Tretten to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tretten is recommended in those who meet the following criteria:

FDA-Approved Indication

40. Congenital Factor XIII A-Subunit Deficiency. Approve for 1 year if the agent is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tretten is not recommended in the following situations:

58. Congenital Factor XIII B-Subunit Deficiency. Tretten will not work in patients who only lack Factor XIII-B subunit.[1,2]

59. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

164. Tretten® injection for intravenous use [prescribing information]. Plainsboro, NJ: Novo Nordisk; June 2020.
165. Menegatti M, Peyvandi F. Treatment of rare factor deficiencies other than hemophilia. *Blood*. 2019;133(5):415-424.
166. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders (Revised February 2020). MASAC Document #259. Adopted on March 16, 2020. Available at: https://www.hemophilia.org/node/3675. Accessed on September 7, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	09/11/2019
Annual revision	No criteria changes.	09/09/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Vonvendi Prior Authorization Policy

- Vonvendi® (von Willebrand factor [recombinant] injection for intravenous use – Baxalta)

REVIEW DATE: 09/09/2020

OVERVIEW

Vonvendi, a recombinant von Willebrand factor (VWF), is indicated for use in adults ≥ 18 years of age diagnosed with von Willebrand disease (VWD) for:[1]

- **On-demand treatment and control** of bleeding episodes.
- **Perioperative management** of bleeding.

Disease Overview

VWD is an inherited bleeding disorder caused by a deficiency or impairment of a protein found in blood called VWF. VWF is a plasma protein with a dual role in hemostasis by mediating platelet adhesion at sites of vascular injury and by binding and stabilizing factor VIII. The disease is rather common as it affects 1 in 100 people; both genders are impacted equally. Symptoms of VWD include mucocutaneous bleeding and excessive hemorrhage following invasive procedures; occasionally, soft tissue hematomas and joint bleeding may also occur. Women who have VWD may experience heavy menorrhagia or experience excessive bleeding at childbirth. Bleeding episodes may be life-threatening in patients with severe forms of VWD. VWD is classified into six types (1, 2A, 2B, 2M, 2N, and 3) according to distinct genotypic, clinical, and laboratory phenotypic characteristics. Type 1 VWD is the most common type (60% to 80% of patients)[4] and represents a partial quantitative deficiency of VWF. Bleeding symptoms are generally mild to moderate.[5] Type 2 VWD affects 15% to 30% of patients and consists of four disease subtypes (2A,

2B, 2M, and 2N) dependent on the specific gene mutation (e.g., decreased VWF-dependent platelet adhesion, decreased binding affinity for factor VIII). This type is due to a qualitative VWF defect and the bleeding is generally moderate, but can vary among patients. Type 3 VWD is uncommon (5% to 10% of patients)[4] but is usually severe because it is due to a virtually complete deficiency of VWF.[5] Many patients with VWD also have reduced factor VIII levels. Treatment options for VWD include desmopressin either parenterally or by a highly concentrated nasal spray (Stimate), Vonvendi, or plasma-derived Factor VIII product that contain VWF.

Guidelines

The National Hemophilia Foundation Medical and Scientific Advisory Council has guidelines for the treatment of hemophilia and other bleeding disorders (revised February 2020).[3] Most patients with type 1 VWD may be treated with a desmopressin product (DDAVP injection or Stimate nasal spray). Some patients with type 2A VWD may respond to DDAVP; a clinical trial with DDAVP should be performed to determine if DDAVP can be used for these particular patients. The guidelines recommend that both DDAVP injection and Stimate not be used in children aged < 2 years and in patients with VWD in whom desmopressin does not provide adequate VWF levels. Also, they should be used cautiously in pregnant women during labor and deliver. Use of plasma-derived VWF-containing Factor VIII concentrates that have VWF is recommended in certain types of VWD that do not respond to therapy with desmopressin (i.e., type 2B VWD and type 3 VWD). Also, plasma-derived Factor VIII concentrates that contain VWF are recommended in types 1, 2A, 2M, and 2N VWD who have become transiently unresponsive to DDAVP, as well as in surgical situations, especially in young children < 2 years of age. Alphanate, Humate-P, and Wilate are indicated for use in VWD; in certain patients Koāte®– DVI (antihemophilic Factor [plasma-derived] injection) may also be effective. Use of cryoprecipitate is not recommended as it has not undergone any viral attenuation steps. Cryoprecipitate should not be utilized to treat patients with VWD except in life- and limb-threatening emergencies when VWD-containing factor VIII concentrate is not immediately available. Vonvendi is available to treat patients with Type 2B and Type 3 VWD; it can also be used in patients with Types 1, 2A, 2M, and 2N VWD who are not responsive to DDAVP and in children < 2 years of age, regardless of VWD type. It contains ultra-large VWF multimers, in addition to the high, medium, and low molecular weight VWF multimers normally found in plasma. Trace amounts of recombinant Factor VIII is in the product as well.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Vonvendi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vonvendi as well as the monitoring required for adverse events and long-term efficacy, approval requires Vonvendi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vonvendi is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Von Willebrand Disease.** Approve for 1 year if the agent is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vonvendi is not recommended in the following situations:

60. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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168. Gill JC, Castaman G, Windyga J, et al. Hemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease. *Blood*. 2015;126(17):2038-2046.
169. Franchini M, Mannucci PM. Von Willebrand factor (Vonvendi®): the first recombinant product licensed for the treatment of von Willebrand disease. *Expert Rev Hematol*. 2016;9(9):825-830.
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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	09/11/2019
Annual revision	No criteria changes.	09/09/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hemophilia – Eptacog Products – NovoSeven RT Prior Authorization Policy

- NovoSeven® RT (Coagulation Factor VIIa [recombinant] for intravenous use – Novo Nordisk)

REVIEW DATE: 10/28/2020

OVERVIEW

NovoSeven RT is indicated for the treatment of bleeding episodes and perioperative management in the following conditions:

- **Congenital Factor VII deficiency** in adults and children;
- **Glanzmann's thrombasthenia** with refractoriness to platelet transfusions in adults and children, with or without antibodies to platelets;
- **Hemophilia, acquired** in adults; and
- **Hemophilia A or B with inhibitors** in adults and children.[1]

Of note, off-label use of NovoSeven RT in the general population has been suggested in a variety of acute bleeding scenarios (e.g., trauma, intracranial hemorrhage). A 2012 Cochrane Review concluded that the effectiveness of recombinant activated Factor VIIa as a general hemostatic drug in non-hemophiliac patients remains unproven and that use outside its licensed indications should be limited to clinical trials.[2] Various reviews and clinical practice guidelines concur that the evidence is insufficient to support use of NovoSeven RT as a hemostatic agent outside of its labeled uses.[3-5]

Guidelines

The National Hemophilia Foundation Medical and Scientific Advisory Council (MASAC) guidelines (updated February 2020) support NovoSeven RT as a treatment option for inherited **hemophilia A or B with inhibitors**, **acquired hemophilia A** (other forms of acquired hemophilia not addressed), and **Factor VII deficiency**.[6] Glanzmann's thrombasthenia is not addressed in the guideline. MASAC recommendations (2013) also state that NovoSeven RT has demonstrated efficacy and safety for prophylactic use for patients with inhibitors in hemophilia A and hemophilia B.[7]

Regarding **hemophilia A and B with inhibitors**, World Federation of Hemophilia guidelines (2020) support recombinant Factor VIIa for patients with high-titer inhibitors who require acute treatment or around surgery/invasive procedures.[8] For low-titer inhibitors, Factor VIII or IX replacement may be used. These products may also be used for patients with a history of a high-titer inhibitor whose titer has fallen to low or undetectable levels. However, once an anamnestic response occurs, further treatment with Factor replacement is typically no longer effective, and bypass agent therapy (e.g., recombinant Factor VIIa) is needed. National Hemophilia Foundation MASAC guidelines (updated February 2020) have similar recommendations: treatment for patients with inhibitors depends on multiple factors, including type of inhibitor (high- or low-responding), current titer, location of bleed, and previous response.[6]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of NovoSeven RT. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with NovoSeven RT as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of NovoSeven RT is recommended in those who meet the following criteria:

FDA-Approved Indications

41. Congenital Factor VII Deficiency. Approve for 1 year if NovoSeven RT is prescribed by or in consultation with a hemophilia specialist.

42. Glanzmann's Thrombasthenia. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient is refractory to platelet transfusions; AND
- **B)** NovoSeven RT is prescribed by or in consultation with a hematologist.

43. Hemophilia, Acquired. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** NovoSeven RT is prescribed by or in consultation with a hemophilia specialist.

44. Hemophilia A with Inhibitors. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient meets one of the following (i, ii, or iii):
  - **i.** Patient has a positive inhibitor titer ≥ 5 Bethesda Units; OR
  - **ii.** Patient has a history of an inhibitor with anamnestic response to Factor VIII replacement therapy, which, according to the prescriber, precludes the use of Factor VIII replacement to treat bleeding episodes; OR
  - **iii.** Patient has a history of an inhibitor with refractory hemostatic response to increased Factor VIII dosing, which, according to the prescriber, precludes the use of Factor VIII replacement to treat bleeding episodes; AND
- **B)** NovoSeven RT is prescribed by or in consultation with a hemophilia specialist.

45. Hemophilia B with Inhibitors. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient meets one of the following (i, ii, or iii):
  - **i.** Patient has a positive inhibitor titer ≥ 5 Bethesda Units; OR
  - **ii.** Patient has a history of an inhibitor with anamnestic response to Factor IX replacement therapy, which, according to the prescriber, precludes the use of Factor IX replacement to treat bleeding episodes; OR
  - **iii.** Patient has a history of an inhibitor with refractory hemostatic response to increased Factor IX dosing, which, according to the prescriber, precludes the use of Factor IX replacement to treat bleeding episodes; AND
- **B)** NovoSeven RT is prescribed by or in consultation with a hemophilia specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of NovoSeven RT is not recommended in the following situations:

61. Bleeding Associated with Liver Disease. Randomized trials have failed to show benefit of NovoSeven RT in controlling upper gastrointestinal bleeding and variceal bleeding in patients with advanced liver disease.[9,10] American Association for the Study of Liver Disease guidelines for portal hypertensive bleeding in cirrhosis (2016) state that recombinant Factor VIIa should not be used to correct coagulopathy in this scenario.[11]

62. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

172. NovoSeven® RT for intravenous use [prescribing information]. Plainsboro, NJ: Novo Nordisk; January 2019.
173. Simpson E, Lin Y, Stanworth S, et al. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. *Cochrane Database Syst Rev.* 2012;3:CD005011.
174. Cannon JW, Khan MA, Raja AS, et al. Damage control resuscitation in patients with severe traumatic hemorrhage: a practice management guideline from the Eastern Association for the Surgery of Trauma. *J Trauma Acute Care Surg.* 2017;82(3):605-617.
175. Hemphill JC 3rd, Greenberg SM, Anderson CS, et al.; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2015;46(7):2032-60.
176. Yank V, Tuohy CV, Logan AC, et al. Comparative effectiveness of in-hospital use of recombinant factor VIIa for off-label indications vs. usual care [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US). Updated May 2010. Available at: https://www.ncbi.nlm.nih.gov/books/NBK98697/. Accessed on July 3, 2019.
177. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders (Revised April 2018). MASAC Document #263. Adopted on September 3, 2020. Available at: https://www.hemophilia.org/node/3675. Accessed on October 12, 2020.
178. MASAC (Medical and Scientific Advisory Council) recommendation regarding prophylaxis with bypassing agents in patients with hemophilia and high titer inhibitors. MASAC Document #220. Adopted on October 6, 2013. Available at: https://www.hemophilia.org/sites/default/files/document/files/masac220.pdf. Accessed on October 12, 2020.
179. Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia*. 2020;26 Suppl 6:1-158.
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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/02/2019
Annual Revision	Policy renamed to "Hemophilia – Eptacog Products – NovoSeven RT". In addition, the following changes were made: **Glanzmann's Thrombasthenia:** Added criterion that the patient be refractory to platelet transfusions, based on product labeling. **Hemophilia, Acquired:** Approval condition renamed to "Hemophilia, Acquired" to align with product labeling. An age criterion of ≥ 18 years of age was added in alignment with product labeling. **Hemophilia A with Inhibitors** and **Hemophilia B with Inhibitors:** Criteria were added requiring an inhibitor titer of ≥ 5 Bethesda Units, anamnestic response to Factor replacement, or refractoriness to increased Factor dosing.	10/28/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hemophilia – Eptacog Products – Sevenfact Prior Authorization Policy

- Sevenfact® (Factor VIIa [recombinant]-jncw for intravenous infusion – LFB S.A./Hema Biologics)

REVIEW DATE: 10/07/2020

OVERVIEW

Sevenfact, a recombinant Factor VIIa product, is indicated for the treatment and control of bleeding episodes occurring in adults and adolescents (≥ 12 years of age) with hemophilia A or B with inhibitors.[1] As a limitation of use, Sevenfact is not indicated for the treatment of patients with congenital Factor VII deficiency.

Disease Overview

Hemophilia is the most common severe hereditary hemorrhagic disorder.[3] It is inherited in an X-linked recessive fashion; thus, males are much more commonly affected. Of note, approximately 30% of hemophilia cases result from spontaneous mutation with no family history. Hemophilia A (Factor VIII deficiency) is the most common form (80% to 85% of total hemophilia cases) and occurs in 1:5,000 live male births. Hemophilia B (Factor IX deficiency) occurs in 1:30,000 live male births.

Antibodies to exogenous clotting factor, known as "inhibitors", may develop. Approximately 30% of patients with severe hemophilia A and up to 5% of patients with severe hemophilia B develop inhibitors to Factor VIII or Factor IX during their lifetime.[4] A high-responding inhibitor (≥ 5 Bethesda Units [BU]) tends to be persistent, whereas low-responding inhibitors of < 5 BU may wane without changes to the treatment regimen. Presence of inhibitors is associated with higher disease burden, increased risk of musculoskeletal complications, pain, physical limitations, and treatment challenges.[4,5]

Guidelines

Sevenfact is not specifically addressed in hemophilia guidelines; recombinant Factor VIIa is referenced more generally. World Federation of Hemophilia (WFH) guidelines (2020) support recombinant Factor VIIa for patients with high-titer inhibitors who require acute treatment or around surgery/invasive procedures.[5] For low-titer inhibitors, Factor VIII or IX replacement may be used. These products may also be used for patients with a history of a high-titer inhibitor whose titer has fallen to low or undetectable levels. However, once an anamnestic response occurs, further treatment with Factor replacement is typically no longer effective, and bypass agent therapy (e.g., recombinant Factor VIIa) is needed. National Hemophilia Foundation MASAC guidelines (updated February 2020) have similar recommendations: treatment for patients with inhibitors depends on multiple factors, including type of inhibitor (high- or low-responding), current titer, location of bleed, and previous response.[7]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Sevenfact. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Sevenfact as well as the monitoring required for adverse events and long-term efficacy, approval requires Sevenfact to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sevenfact is recommended in those who meet the following criteria:

FDA-Approved Indications

46. Hemophilia A with Inhibitors. Approve for 1 year if the patient meets all of the following (A, B, and C):
- **A)** Patient is ≥ 12 years of age; AND
- **B)** Patient meets one of the following (i, ii, or iii):
  - **i.** Patient has a positive inhibitor titer ≥ 5 Bethesda Units; OR
  - **ii.** Patient has a history of anamnestic response to Factor VIII replacement therapy, which, according to the prescriber, precludes the use of Factor VIII replacement to treat bleeding episodes; OR
  - **iii.** Patient has a history of refractory response to increased Factor VIII dosing, which, according to the prescriber, precludes the use of Factor VIII replacement to treat bleeding episodes; AND
- **C)** Sevenfact is prescribed by or in consultation with a hemophilia specialist.

47. Hemophilia B with Inhibitors. Approve for 1 year if the patient meets all of the following (A, B, and C):
- **A)** Patient is ≥ 12 years of age; AND
- **B)** Patient meets one of the following (i, ii, or iii):
  - **i.** Patient has a positive inhibitor titer ≥ 5 Bethesda Units; OR
  - **ii.** Patient has a history of anamnestic response to Factor IX replacement therapy, which, according to the prescriber, precludes the use of Factor IX replacement to treat bleeding episodes; OR
  - **iii.** Patient has a history of refractory response to increased Factor IX dosing, which, according to the prescriber, precludes the use of Factor IX replacement to treat bleeding episodes; AND
- **C)** Sevenfact is prescribed by or in consultation with a hemophilia specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sevenfact is not recommended in the following situations:

63. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/07/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hemophilia – Factor IX Products

EXTENDED HALF-LIFE RECOMBINANT PRODUCTS

- Alprolix® (Coagulation Factor IX [recombinant] Fc fusion protein injection – Bioverativ)
- Idelvion (Coagulation Factor IX [recombinant] albumin fusion protein injection – CSL Behring)
- Rebinyn® (Coagulation Factor IX [recombinant] glycoPEGylated injection – NovoNordisk)

Standard Half-Life Recombinant Products

- BeneFIX® (Coagulation Factor IX [recombinant] injection – Wyeth/Pfizer)
- Ixinity® (Coagulation Factor IX [recombinant] injection – Aptevo BioTherapeutics)
- Rixubis® (Coagulation Factor IX [recombinant] injection – Baxalta)

Plasma-Derived Products

- AlphaNine® SD (Coagulation Factor IX [plasma-derived] injection – Grifols)
- Mononine® (Coagulation Factor IX [plasma-derived] injection – CSL Behring)
- Profilnine® (Factor IX Complex [plasma-derived] injection – Grifols)

REVIEW DATE: 02/19/2020

OVERVIEW

Alprolix, Idelvion, and Rebinyn are extended half-life recombinant Factor IX products indicated in adults and children with hemophilia B for on-demand treatment and control of bleeding episodes and perioperative management of bleeding.[1-3] Alprolix and Idelvion are also indicated for routine prophylaxis to reduce the frequency of bleeding episodes. BeneFIX and Ixinity are standard half-life recombinant Factor IX products that are indicated for the control and prevention of bleeding episodes in adult and pediatric patients (≥ 12 years of age for Ixinity) with hemophilia B, as well as for perioperative management.[4,5] Rixubis is indicated for use in adults and children with hemophilia B for on-demand treatment and control of bleeding episodes; perioperative management of bleeding; and routine prophylaxis to reduce the frequency of bleeding episodes.[6] AlphaNine SD, Mononine, and Profilnine plasma-derived Factor IX products that are indicated for the prevention and control of bleeding in patients with Factor IX deficiency due to hemophilia B.[7-9]

Disease Overview

Hemophilia B is a recessive X-linked bleeding disorder caused by mutations in the factor IX gene that leads to the deficiency or absence of the coagulation factor IX.[10,11] It occurs in 1 out of 30,000 male births and affects about 5,000 people in the US. Hemophilia B predominantly occurs in males; however, approximately 10% of females are carriers and are at risk of usually mild bleeding. The severity of bleeding depends on the degree of the factor IX defect and the phenotypic expression. Factor levels of <1%, 1% to 5%, and > 5% to < 40% are categorized as severe, moderate, and mild hemophilia B, respectively. Patients with mild hemophilia B may only experience abnormal bleeding during surgery, during tooth extractions, or when injured. Patients with moderate hemophilia B generally have prolonged

bleeding responses to minor trauma. Severe hemophilia B is marked by spontaneous bleeding such as spontaneous hemarthrosis, soft-tissue hematomas, retroperitoneal bleeding, intracerebral hemorrhage, and delayed bleeding post-surgery. Complications from recurrent bleeding and soft-tissue hematomas include severe arthropathy, and joint contractures, which may lead to pain and disability. The main treatment of hemophilia B is replacement of missing blood coagulation with Factor IX products. Factor IX replacement therapy may be used on-demand when bleeding occurs or given as routine prophylaxis with scheduled infusions. Both plasma-derived and recombinant Factor IX products are available. In general, prophylactic therapy has been associated with a reduction in bleeds and improved outcomes for selected patients (e.g., patients with moderate or severe factor IX deficiency). The goal of therapy is to prevent uncontrolled internal hemorrhage and severe joint damage and to properly manage bleeding episodes. The development of inhibitors occurs at a lower frequency in patients with severe hemophilia B compared with severe hemophilia A but can occur in up to 5% of patients. Higher doses than that typically used for these uses of standard half-life products can be given if the patient develops an inhibitor.

Guidelines

In April 2018, the Medical and Scientific Council (MASAC) from the National Hemophilia Foundation (NHF) updated recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders.[12] The guidelines discuss Factor IX products. Due to safety issues, recombinant Factor IX is the treatment of choice for patients in the management of hemophilia B. Regarding plasma-derived Factor IX concentrates, improved viral-depleting processes and donor screening practices have led to plasma-derived Factor IX products that have a greatly reduced risk for transmission of human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV). Due to higher purity and only limited amounts of other factors contained in the products, AlphaNine SD and Mononine are the human plasma-derived products that are considered to be of high purity and are recognized options by MASAC in the management of hemophilia B. Profilnine is used in patients with Factor II and/or X deficiency.[12] Some data are available, albeit limited.[13]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of the following Factor IX products: Alprolix, Idelvion, Rebinyn, BeneFIX, Ixinity, Rixubis, AlphaNine, Mononine, and Profilnine. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with recombinant Factor IX products, as well as the monitoring required for adverse events and long-term efficacy, the agent is required to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Alprolix, Idelvion, Rebinyn, BeneFIX, Ixinity, and Rixubis is recommended for patients who meet the following criteria:

FDA-Approved Indications

48. Hemophilia B. Approve for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

II. Coverage of AlphaNine SD, Mononine, and Profilnine is recommended for patients who meet the following criteria:

FDA-Approved Indications

1. Hemophilia B. Approve for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

III. Coverage of Profilnine is recommended for patients who meet the following criteria:

Other Uses with Supportive Evidence

2. **Factor II Deficiency.** Approve Profilnine for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

3. **Factor X Deficiency.** Approve Profilnine for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of the cited Factor IX products is not recommended in the following situations:

64. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Alprolix® lyophilized powder for intravenous injection [prescribing information]. Waltham, MA: Bioverativ; October 2019.
2. Idelvion® lyophilized powder for solution for intravenous injection [prescribing information]. Kankakee, IL: CSL Behring; October 2019.
3. Rebinyn® lyophilized powder for solution for intravenous injection [prescribing information]. Plainsboro, NJ: Novo Nordisk; May 2017.
4. BeneFIX® injection for intravenous use [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc. (a subsidiary of Pfizer); July 2019.
5. Ixinity® solution for intravenous injection [prescribing information]. Seattle, WA: Aptevo BioTherapeutics; December 2018.
6. Rixubis® for intravenous injection [prescribing information]. Lexington, MA: Baxalta; December 2019.
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HISTORY

Type of Revision	Summary of Changes	Review Date
New policy	--	02/27/2019
Annual revision	No criteria changes.	02/19/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hemophilia – Factor VIII Products

Extended Half-Life Products

- Adynovate® (Antihemophilic Factor PEGylated injection – Baxalta)
- Eloctate® (Antihemophilic Factor Fc fusion protein injection – Bioverativ)
- Esperoct® (Antihemophilic factor glycopegylated injection – Novo Nordisk)
- Jivi® (Antihemophilic Factor PEGylated-aucl injection – Bayer HealthCare)

Standard Half-Life Products

- Advate® (Antihemophilic Factor injection – Baxalta)

- Afstyla® (Antihemophilic Factor single chain injection – CSL Behring)
- Helixate® FS (Antihemophilic Factor injection – Bayer HealthCare/CSL Behring)
- Kogenate® FS (Antihemophilic Factor injection – Bayer HealthCare)
- Kovaltry® (Antihemophilic Factor injection – Bayer HealthCare)
- Novoeight® (Antihemophilic Factor injection – Novo Nordisk)
- Nuwiq® (Antihemophilic Factor injection – Octapharma)
- Recombinate® (Antihemophilic Factor injection –Baxalta)
- Xyntha®/Xyntha® Solofuse™ (Antihemophilic Factor injection, plasma/albumin-free – Wyeth/Pfizer)

Plasma-Derived Standard Half-Life Products without Von Willebrand Factor

- Hemofil® M (Antihemophilic Factor injection –Baxalta)
- Monoclate-P® (Antihemophilic Factor injection – CSL Behring)

Plasma-Derived Standard Half-Life Products with Von Willebrand Factor

- Alphanate® (Antihemophilic Factor/von Willebrand Factor Complex [human] injection – Grifols)
- Humate-P® (Antihemophilic Factor/von Willebrand Factor Complex injection – CSL Behring)
- Koāte® (Antihemophilic Factor injection – Grifols/Kedrion Biopharma)
- Wilate® (von Willebrand Factor/Coagulation Factor VIII Complex for intravenous use – Octapharma)

REVIEW DATE: 02/19/2020

OVERVIEW

For the management of hemophilia A, many recombinant Factor VIII products are available, including extended half-life products[1-4] (Adynovate, Eloctate, Esperoct, and Jivi) as well as standard half-life products (Advate, Afstyla, Helixate, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, and Xyntha).[5-16] In general, such products are used for the on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and for routine prophylaxis to reduce the frequency of bleeding episodes. Several standard half-life Factor VIII plasma-derived products are available. Hemofil M and Monoclate P are plasma-derived standard half-life products that do not contain substantial amounts of von Willebrand Factor which are indicated in hemophilia A (classical hemophilia) for the prevention and control of hemorrhagic episodes.[17,18] Plasma-derived Factor VIII products that contain von Willebrand Factor include Alphanate, Humate P, Koate, and Wilate.[19-22] Alphanate is indicated for the control and prevention of bleeding in adult and pediatric patients with hemophilia A.[1] Alphanate is also indicated for surgical and/or invasive procedures in adult and pediatric patients with von Willebrand Disease in whom desmopressin is either ineffective or contraindicated. The agent is not indicated for patients with severe von Willebrand Disease (type 3) undergoing major surgery.[19] Humate-P is indicated for the treatment and prevention of bleeding in adults with hemophilia A (classical hemophilia).[20] Humate P is also indicated in adult and pediatric patients with von Willebrand disease for the treatment of spontaneous and trauma-induced bleeding episodes and for the prevention of excessive bleeding during and after surgery. The indication in von Willebrand Disease applies to patients with severe von Willebrand disease, as well as in patients with mild to moderate von Willebrand disease where use of desmopressin is known or suspected to be inadequate. Koate is indicated for the control and prevention of bleeding episodes or in order to perform emergency elective surgery in patients with hemophilia A.[21] Wilate is indicated in children and adults with von Willebrand disease for on-demand treatment and control of bleeding episodes and for perioperative management of bleeding.[22] Wilate is also indicated in adolescents and adults with hemophilia A for routine prophylaxis to reduce the frequency of bleeding episodes and on-demand treatment and control of bleeding episodes.

Disease Overview

Hemophilia A is an X-linked bleeding disorder caused by a deficiency in Factor VIII.[23-25] In the US, the incidence of hemophilia A in males is 1:5,000 with an estimated 20,000 people in the US living with hemophilia A. Sometimes the disorder is caused by a spontaneous genetic mutation. Males primarily have the disorder and most times females are asymptomatic carriers. The condition is characterized by bleeding in joints, either spontaneously or in a provoked joint. Bleeding can occur in many different body areas (e.g., muscles, central nervous system, gastrointestinal). Hemarthrosis is the main sign of hemophilia in older children and adults. In newborns and toddlers, bleeding in the

head (intracranial hemorrhage and extracranial hemorrhage), bleeding from circumcision, and in the oral cavity are more common. The bleeding manifestations can lead to substantial morbidity, as well as mortality, if not properly treated. Disease severity is usually defined by the plasma levels of Factor VIII and have been classified as follows: severe (levels less than 1% of normal [normal plasma levels are 50 to 100 U/dL]), moderate (levels 1% to 5% of normal), and mild (levels > 5%); phenotypic expression may also vary. Approximately 25% to 30% of patients with hemophilia A have severe deficiency whereas 3% to 13% of patients have moderate to mild deficiency. Diagnoses can be substantially delayed, especially in patients with mild disease, as bleeding may not clinically occur. Higher doses than that typically used for these uses of standard half-life products can be given if the patient develops an inhibitor, which develop in approximately 25% of patients.[26]

Von Willebrand Disease is a group of inherited bleeding disorders related to defects of von Willebrand Factor (vWF), which is needed to achieve hemostasis.[27-29] It occurs equally in males and females. The disease leads to bleeding from impaired platelet adhesion and aggregation, which may be accompanied by reduced levels of factor VIII. Mucous membrane and skin bleeding symptoms, as well as bleeding with surgical or other hematostatic challenges, may occur. The prevalence of the disease is approximately 1.3%. Pregnancy can increase vWF levels and confound diagnosis. The three major subsubtypes of von Willebrand Disease include: partial quantitative vWF deficiency (type 1, 75% of patients); qualitative vWF deficiency (type 2, 25% of patients); and complete vWF deficiency (type 3, rare). Type 2 disease is further divided into four variants (2A, 2B, 2M, 2N) on the basis of the phenotype. In type 3 von Willebrand Disease, Factor VIII levels are usually very low. Acquired von Willebrand syndrome may result but is rare, occurring in fewer than one in 100,000 adults. The bleeding risk varies between modest increases in bleeding which occur only with procedures to a major risk of spontaneous hemorrhage. Approaches to the management of von Willebrand Disease involve increasing plasma concentrations of vWF through stimulation with desmopressin; replacing vWF by using human plasma-derived viral inactivated concentrates; and promoting hemostasis by use of hemostatic agents with mechanisms other than increasing vWF; and Vonvendi® (von Willebrand factor [recombinant] injection for intravenous use). Regular prophylaxis is not frequently required.

Guidelines

The National Hemophilia Foundation (NHF) Medical and Scientific Advisory Council (MASAC) has recommendations concerning products used for the treatment of hemophilia and other bleeding disorders.[23] It is noted that recombinant Factor VIII products are the recommended treatment of choice for patients with hemophilia A. The MASAC recommendations regarding plasma-derived Factor VIII products state that improved viral-depleting processes and donor screening practices have greatly reduced the risk of transmission and human immunodeficiency virus (HIV), hepatitis B (HBV), and hepatitis C virus (HCV).

MASAC recommendations also discuss von Willebrand Disease and vWF-containing Factor VIII products.[23] Most patients with von Willebrand Disease type 1 may be treated with either desmopressin (either parenterally [DDAVP injection] or by a highly concentrated nasal spray [Stimate nasal spray]). For surgery, trauma, or other serious bleeding episodes, if hemostasis is not achieved using DDAVP, a Factor VIII concentrate that contains high molecular weight multimers of vWF should be used. Patients with type 2B and type 3 von Willebrand Disease, and those with type 1, 2A, 2M, and 2N who have not responded adequately to DDAVP should be treated with a Factor VIII concentrate that contains higher molecular weight multimers of vWF. Products FDA-approved for this use include Alphanate, Humate P, and Wilate. Koate may be effective but it not FDA-approved for this use.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of the following Factor VIII products: Adynovate, Eloctate, Esperoct, Jivi, Advate, Afstyla, Helixate FS, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, Xyntha, Hemofil M, Monoclate P, Alphanate, Humate-P, Koate, and Wilate. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with recombinant Factor VIII products, as well as the monitoring required for adverse events and long-term efficacy, the agent is required to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Adynovate, Eloctate, Esperoct, Jivi, Advate, Afstyla, Helixate FS, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, and Xyntha is recommended in those who meet one of the following criteria.

FDA-Approved Indications

49. Hemophilia A. Approve the requested agent for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

II. Coverage of Hemofil M, Monoclate-P, Alphanate, Humate-P, Koate, and Wilate is recommended in those who meet one of the following criteria:

1. Hemophilia A. Approve the requested agent for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

2. Von Willebrand Disease. Approve for 1 year if the agent is prescribed by or in consultation with a hemophilia specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Factor VIII products is not recommended in the following situations:

65. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

189. Adynovate® lyophilized powder for solution for intravenous injection [prescribing information]. Lexington, MA: Baxalta; May 2018.
190. Eloctate® lyophilized powder for solution for intravenous injection [prescribing information]. Waltham, MA: Bioverativ; September 2019.
191. Jivi® lyophilized powder for solution for intravenous use [prescribing information]. Whippany, NJ: Bayer HealthCare; August 2018.
192. Esperoct® lyophilized powder for solution for intravenous use [prescribing information]. Plainsboro, NJ: Novo Nordisk; October 2019.
193. Advate® lyophilized powder for reconstitution for intravenous injection [prescribing information]. Westlake Village, CA: Baxalta/Shire; December 2018.
194. Kovaltry® lyophilized powder for solution for intravenous injection [prescribing information]. Whippany, NJ: Bayer HealthCare; March 2016.
195. Afstyla® lyophilized powder for solution for intravenous injection [prescribing information]. Kankakee, IL: CSL Behring; December 2019.
196. Helixate® FS lyophilized powder for reconstitution for intravenous use [prescribing information]. Kankakee, IL and Whippany, NJ: CSL Behring and Bayer HealthCare; May 2016.
197. Kogenate® FS lyophilized powder for reconstitution for intravenous use [prescribing information]. Whippany, NJ: Bayer HealthCare; May 2016.
198. Kogenate® FS lyophilized powder for reconstitution with vial adapter for intravenous use [prescribing information]. Whippany, NJ: Bayer HealthCare; May 2016.
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200. Novoeight® lyophilized powder for solution for intravenous injection [prescribing information]. Plainsboro, NJ: Novo Nordisk; November 2018.
201. Nuwiq® lyophilized powder solution for intravenous injection [prescribing information]. Hoboken, NJ: Octapharma; July 2017.

202. Recombinate™ lyophilized powder for reconstitution for injection [prescribing information]. Lexington, MA: Baxalta; June 2018.
203. Xyntha® lyophilized powder for solution intravenous injection [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals (a subsidiary of Pfizer); October 2014.
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207. Alphanate® for intravenous injection [prescribing information]. Los Angeles, CA: Grifols; June 2018.
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209. Koāte for intravenous injection [prescribing information]. Fort Lee, NJ and Research Triangle Park, NC: Kedrion Biopharmaand Grifols; June 2018.
210. Wilate® lyophilized powder for solution for intravenous injection [prescribing information]. Hoboken, NJ: Octapharma; September 2019.
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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	02/27/2019
Annual Revision	No criteria changes.	02/19/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hemophilia – FEIBA Prior Authorization Policy

- Hemophilia – FEIBA® (anti-inhibitor coagulant complex for intravenous use – Takeda)

REVIEW DATE: 10/28/2020

OVERVIEW

FEIBA, a human plasma fraction with Factor VIII bypassing activity, is indicated for use in **hemophilia A and B patients with inhibitors for control and prevention of bleeding episodes, perioperative management, and routine prophylaxis** to prevent or reduce the frequency of bleeding episodes.[1] It contains both activated and inactivated forms of Factors II, VII, IX, and X and is thus referred to as activated prothrombin complex concentrate (aPCC).[1,2] FEIBA is produced from pooled human plasma.[1]

Guidelines

Regarding **hemophilia A with inhibitors** and **hemophilia B with inhibitors** (without history of anaphylaxis/allergy to Factor IX), World Federation of Hemophilia guidelines (2020) support aPCC for patients with high-titer inhibitors who require acute treatment or around surgery/invasive procedures.[3] For low-titer inhibitors, Factor VIII or IX replacement may be used. These products may also be used for patients with a history of a high-titer inhibitor whose titer has fallen to low or undetectable levels. However, once an anamnestic response occurs, further treatment with

Factor replacement is typically no longer effective, and bypass agent therapy (e.g., aPCC) is needed. National Hemophilia Foundation Medical and Scientific Advisory Council (MASAC) guidelines (updated February 2020) have similar recommendations: treatment for patients with inhibitors depends on multiple factors, including type of inhibitor (high- or low-responding), current titer, location of bleed, and previous response.[2]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of FEIBA. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with FEIBA as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of FEIBA is recommended in those who meet the following criteria:

FDA-Approved Indications

50. Hemophilia A with Inhibitors. Approve for 1 year if the patient meets the following criteria (A and B):

- **A)** Patient meets one of the following (i, ii, or iii):
  - **i.** Patient has a positive inhibitor titer ≥ 5 Bethesda Units; OR
  - **ii.** Patient has a history of an inhibitor with anamnestic response to Factor VIII replacement therapy, which, according to the prescriber, precludes the use of Factor VIII replacement to treat bleeding episodes; OR
  - **iii.** Patient has a history of an inhibitor with refractory hemostatic response to increased Factor VIII dosing, which, according to the prescriber, precludes the use of Factor VIII replacement to treat bleeding episodes; AND
- **B)** FEIBA is prescribed by or in consultation with a hemophilia specialist.

51. Hemophilia B with Inhibitors. Approve for 1 year if the patient meets the following criteria (A and B):

- **A)** Patient meets one of the following (i, ii, or iii):
  - **i.** Patient has a positive inhibitor titer ≥ 5 Bethesda Units; OR
  - **ii.** Patient has a history of an inhibitor with anamnestic response to Factor IX replacement therapy, which, according to the prescriber, precludes the use of Factor IX replacement to treat bleeding episodes; OR
  - **iii.** Patient has a history of an inhibitor with refractory hemostatic response to increased Factor IX dosing, which, according to the prescriber, precludes the use of Factor IX replacement to treat bleeding episodes; AND
- **B)** FEIBA is prescribed by or in consultation with a hemophilia specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of FEIBA is not recommended in the following situations:

66. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

218. FEIBA® for intravenous use [prescribing information]. Lexington, MA: Shire/Takeda; December 2018.

219. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders (Revised April 2018). MASAC Document #263. Adopted on September 3, 2020. Available at: https://www.hemophilia.org/node/3675. Accessed on October 12, 2020.
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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/02/2019
Annual Revision	**Hemophilia A with Inhibitors** and **Hemophilia B with Inhibitors:** Criteria were added requiring an inhibitor titer of ≥ 5 Bethesda Units, anamnestic response to Factor replacement, or refractoriness to increased Factor dosing.	10/28/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hemophilia – Hemlibra Prior Authorization Policy
- Hemlibra® (emicizumab-kxwh injection for subcutaneous use – Genentech/Roche/Chugai)

REVIEW DATE: 12/02/2020

OVERVIEW

Hemlibra, a bispecific Factor IXa- and Factor X-directed antibody, is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients aged newborn and older with **hemophilia A** (congenital factor VIII deficiency) with or without factor VIII inhibitors.[1]

Disease Overview

Hemophilia A is an X-linked bleeding disorder caused by a deficiency in Factor VIII.[2-4] In the US, the incidence of hemophilia A in males is 1:5,000 with an estimated 20,000 people in the US living with hemophilia A. Sometimes the disorder is caused by a spontaneous genetic mutation. Males primarily have the disorder and most times females are asymptomatic carriers. The condition is characterized by bleeding in joints, either spontaneously or in a provoked joint. Bleeding can occur in many different body areas (e.g., muscles, central nervous system, gastrointestinal). Hemarthrosis is the main sign of hemophilia in older children and adults. In newborns and toddlers, bleeding in the head (intracranial hemorrhage and extracranial hemorrhage), bleeding from circumcision, and in the oral cavity are more common. The bleeding manifestations can lead to substantial morbidity, as well as mortality, if not properly treated. Disease severity is usually defined by the plasma levels of Factor VIII and have been classified as follows: severe (levels less than 1% of normal [normal plasma levels are 50 to 100 U/dL]), moderate (levels 1% to 5% of normal), and mild (levels > 5%); phenotypic expression may also vary. Approximately 25% to 30% of patients with hemophilia A have severe deficiency whereas 3% to 13% of patients have moderate to mild deficiency. Diagnoses can be substantially delayed, especially in patients with mild disease, as bleeding may not clinically occur. Higher doses than that typically used for these uses of standard half-life products can be given if the patient develops an inhibitor, which develop in approximately 25% of patients.[5] Products that contains Factor VIII, which are given intravenously, are utilized as well as agents such as Hemlibra.[2-4]

Guidelines

Two documents from the National Hemophilia Foundation Medical and Scientific Advisory Council provide recommendations regarding Hemlibra.[2,6] In general, Hemlibra has been shown to prevent or reduce the occurrence of bleeding in patients with hemophilia A in adults, adolescent, children and infants, both

with and without inhibitors. Subcutaneous administration at more prolonged dosing intervals is viewed as having advantages for some patients compared with intravenous administration of Factor VIII products.

Safety

Hemlibra has a Boxed Warning regarding thrombotic microangiopathy and thromboembolism.[1] Cases of thrombotic microangiopathy are thrombotic events were reported when on average a cumulative amount of > 100 U/kg/24 hours of activated prothrombin complex concentrate (aPCC) was given for 24 hours or more to patients receiving Hemlibra prophylaxis. Monitor for the development of thrombotic microangiopathy and thrombotic events when aPCC is given.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Hemlibra. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Hemlibra is recommended in those who meet the following criteria:

FDA-Approved Indication

46. Hemophilia A. Approve for 1 year if the patient meets the following criteria (A and B):
- **N)** Patient is using Hemlibra for routine prophylaxis; AND
- **O)** Medication is prescribed by or in consultation with a hemophilia specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Hemlibra is not recommended in the following situations:

10. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

181. Hemlibra® injection for subcutaneous use [prescribing information]. South San Francisco, CA and Tokyo, Japan: Genentech/Roche and Chugai Pharmaceutical; June 2020.
182. National Hemophilia Foundation. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders (Revised August 2020). MASAC Document #259. Adopted on August 3, 2020. Available at: https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-263-masac-recommendations-concerning-products-licensed-for-the-treatment-of-hemophilia-and-other-bleeding-disorders. Accessed on November 23, 2020.
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184. Berntorp E, Shapiro. Modern haemophilia care. *Lancet*. 2012;379:1447-1456.
185. Valentino LA, Kempton CL, Kruse-Jarres R, et al, on behalf of the International Immune Tolerance Induction Study Investigators. US guidelines for immune tolerance induction in patients with haemophilia a and inhibitors. *Haemophilia*. 2015;21(5):559-567.
186. National Hemophilia Foundation. MASAC (Medical and Scientific Advisory Council) recommendations on the use and management of emicizumab-kxwh (Hemlibra®) for hemophilia A with and without inhibitors. MASAC Document #258. Adopted on March 16, 2020. Available at: https://www.hemophilia.org/sites/default/files/document/files/258_emicizumab.pdf. Accessed on November 23, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual revision	**Hemophilia A:** Based on the new indication for Hemlibra, removed the criteria that the patients has factor VIII inhibitors or a history of factor VIII inhibitors. The criterion were added that Hemlibra is being utilized for routine prophylaxis.	10/10/2018
Annual Revision	No criteria changes.	10/02/2019
Annual Revision	No criteria changes.	12/02/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hepatitis C – Epclusa Prior Authorization Policy

- Epclusa® (velpatasvir/sofosbuvir tablets – Gilead)
- velpatasvir/sofosbuvir tablets (authorized generic to Epclusa – Gilead)

REVIEW DATE: 06/17/2020

OVERVIEW

Epclusa is a fixed-dose combination of velpatasvir, a hepatitis C virus (HCV) NS5A inhibitor, and sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor, indicated for the treatment of chronic HCV genotype 1 through 6 infection in adult and pediatric patients ≥ 6 years of age or weighing ≥ 17 kg.[1] In patients without cirrhosis or with compensated cirrhosis, Epclusa is indicated alone. In patients with decompensated cirrhosis (Child-Pugh B or C), Epclusa is indicated in combination with ribavirin.

Dosing

The recommended dosage of Epclusa in adults is one tablet (400 mg velpatasvir/100 mg sofosbuvir) taken orally once daily (QD) with or without food.[1] In pediatric patients ≥ 6 years of age or weighing ≥ 17 kg to < 30 kg the recommended dosage of Epclusa is one tablet (200 mg velpatasvir/50 mg sofosbuvir) QD with or without food. In pediatric patients ≥ 6 years of age or weighing ≥ 30 kg the recommended dosage of Epclusa is one tablet (400 mg velpatasvir/100 mg sofosbuvir) or two tablets (200 mg velpatasvir/50 mg sofosbuvir) QD with or without food. In patients with decompensated cirrhosis (Child-Pugh B or C), Epclusa is administered with weight-based ribavirin (WBR). The FDA-approved duration of therapy is 12 weeks for all patients.

Clinical Efficacy

The efficacy of Epclusa for the treatment of genotypes 1 through 6 chronic HCV was established in four published, Phase III clinical trials (ASTRAL-1, -2, -3, and -4).[3-5] In ASTRAL-1, -2, and -3, a total of 1,035 patients received 12 weeks of Epclusa; 21% of patients had compensated cirrhosis and 28% had failed prior therapies for HCV. In the ASTRAL-4 study, 267 patients with decompensated cirrhosis (Child-Pugh B) were randomized to receive 12 or 24 weeks of Epclusa ± WBR. The primary endpoint for all four studies was sustained viral response 12 weeks after treatment completion (SVR12).

In ASTRAL-1 (n = 706), SVR12 was attained in 99% of patients overall with genotypes 1, 2, 4, 5, or 6 chronic HCV treated with Epclusa for 12 weeks. In ASTRAL-2 (n = 269), Epclusa was superior to Sovaldi + WBR in patients with genotype 2 chronic HCV. SVR12 was attained in 99% of patients treated for 12 weeks with Epclusa and in 94% of patients treated with Sovaldi + WBR for 12 weeks. In ASTRAL-3 (n = 558), Epclusa was superior to Sovaldi + WBR in patients with genotype 3 chronic HCV. SVR12 was attained in 95% of patients treated for 12 weeks with Epclusa and in 80% of patients treated with Sovaldi + WBR for 24 weeks.

In ASTRAL-4 (n = 268), Epclusa was administered in one of three regimens in patients with genotypes 1 through 6 chronic HCV with decompensated cirrhosis (Child-Pugh B). SVR12 was attained in 83%, 94%, and 86% of patients treated with Epclusa for 12 weeks, Epclusa + WBR for 12 weeks, and Epclusa for 24 weeks, respectively. The study was not designed to assess differences among treatment groups or by genotype. However, numerically higher rates of SVR12 were generally observed for Epclusa + WBR vs. non-ribavirin containing arms.

For more detailed efficacy information with Epclusa see the *Hepatitis C Virus Direct-Acting Antivirals Therapy Class Summary*.

Guidelines

American Association for the Study of Liver Diseases (AASLD) recommendations provide a simplified treatment algorithm for treatment-naïve adults without cirrhosis as well as for treatment-naïve patients with compensated cirrhosis. In treatment-naïve adults without cirrhosis the recommended regimens are Mavyret for 8 weeks or Epclusa for 12 weeks. In treatment-naïve adults with compensated cirrhosis, the recommended regimens are Mavyret for 8 weeks (genotypes 1 through 6) or Epclusa for 12 weeks (genotypes 1, 2, 4, 5, or 6; patients with genotype 3 require baseline NS5A resistance-associated substitution [RAS] testing and those without Y93H can be treated with 12 weeks of Epclusa). Additional genotype-specific and/or special circumstance-specific recommendations are also provided.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Epclusa (brand or generic). Criteria are based on the guidance issued by American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA, prescribing information, clinical data, and expert review. Because of the specialized skills required for evaluation and diagnosis of patients treated with Epclusa (brand or generic) as well as the monitoring required for adverse events (AEs) and efficacy, approval requires Epclusa (brand or generic) to be prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or liver transplant physician. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Epclusa (brand or generic) is recommended in those who meet the following criteria:

FDA-Approved Indications

37. Chronic Hepatitis C Virus (HCV) Genotype 1, 2, 3, 4, 5, or 6, No Cirrhosis or Compensated Cirrhosis (Child-Pugh A). Approve Epclusa (brand or generic) for 12 weeks if the patient meets all of the following criteria (A, B, C, and D):

- **i.** The patient is ≥ 6 years of age or ≥ 17 kg; AND
- **ii.** Epclusa (brand or generic) is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician; AND
- **iii.** The patient has not been previously treated with Epclusa (brand or generic); AND
- **iv.** The patient does not have cirrhosis OR the patient has compensated cirrhosis (Child-Pugh A)

2. **Chronic Hepatitis C Virus (HCV) Genotype 1, 2, 3, 4, 5, or 6, Decompensated Cirrhosis (Child-Pugh B or C), Adults.** Approve Epclusa (brand or generic) for the specified duration if the patient meets all of the following criteria (A, B, C, D, and E):
   A) The patient is ≥ 18 years of age; AND
   B) Epclusa (brand or generic) is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician; AND
   C) The patient has not been previously treated with Epclusa (brand or generic) or Vosevi (*see Criterion 4*); AND
   D) The patient has decompensated cirrhosis (Child-Pugh B or C); AND
   E) The patient meets one of the following criteria:
      i. The patient is ribavirin-eligible, according to the prescribing physician: Approve Epclusa (brand or generic) for **12 weeks**, if Epclusa (brand or generic) is prescribed **in combination with ribavirin**; OR
      ii. The patient is ribavirin-ineligible, according to the prescribing physician: Approve Epclusa (brand or generic) for **24 weeks**.

3. **Chronic Hepatitis C Virus (HCV) Genotype 1, 2, 3, 5, 6, or 6, Decompensated Cirrhosis (Child-Pugh B or C), Pediatric Patients.** Approve Epclusa (brand or generic) for 12 weeks if the patient meets all of the following criteria (A, B, C, and D):
   A) The patient is ≥ 6 years of age or ≥ 17 kg; AND
   B) Epclusa (brand or generic) is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician; AND
   C) The patient has not been previously treated with Epclusa (brand or generic); AND
   D) The patient has decompensated cirrhosis (Child-Pugh B or C); AND
   E) Epclusa will be prescribed **in combination with ribavirin.**

Other Uses with Supportive Evidence

4. **Chronic Hepatitis C Virus, Genotype 1, 2, 3, 4, 5, or 6, Decompensated Cirrhosis (Child-Pugh B or C), Prior Null Responders, Prior Partial Responders, and Prior Relapsers to Epclusa (brand or generic) or Vosevi.** Approve Epclusa (brand or generic) for 24 weeks in patients who meet all of the following criteria (A, B, C, D, and E).
   A) The patient is ≥ 18 years of age; AND
   B) Epclusa (brand or generic) is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician; AND
   C) The patient has been previously treated with Epclusa (brand or generic) or Vosevi; AND
   D) The patient has decompensated cirrhosis (Child-Pugh B or C); AND
   E) Epclusa (brand or generic) will be prescribed in combination with ribavirin.

   AASLD guidelines recommend Epclusa for 24 weeks in combination with ribavirin for patients with genotypes 1, 2, 3, 4, 5, or 6 chronic HCV who have not responded to treatment with an NS5A inhibitor or sofosbuvir (Level II, C).[2] Data are limited to one Phase II study where Epclusa was studied in patients with genotype 1, 2, and 3 who did not respond to velpatasvir-containing regimens including Epclusa and Vosevi.[2,6] Retreatment with Epclusa + ribavirin for 24 weeks yielded high overall response rates (SVR12 91% [n = 63/69]). Among patients with genotype 1 chronic HCV, 97% of patients (n = 36/37) achieved SVR12. In patients with genotype 2 chronic HCV, SVR12 was attained in 95% of patients (n = 13/14) and in patients with genotype 3 chronic HCV, SVR12 was attained in 78% of patients (n = 14/18). Baseline NS5A resistance associated substitutions (RASs) did not appear to effect SVR rates. No breakdown of the proportion of patients with decompensated cirrhosis was provided in the study.

5. **Patient Has Been Started on Epclusa (brand or generic).** Approve for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications or Other Uses with Supportive Evidence). Approve the duration described above to complete a course therapy (e.g., a patient who should receive 12 weeks, and has received 3 weeks should be approved for 9 weeks to complete their 12-week course).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Epclusa (brand or generic) has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Hepatitis C Virus (HCV) [any genotype], Combination with Any Other Direct-Acting Antivirals (DAAs) [Not Including Ribavirin].** Epclusa (brand or generic) provides a complete antiviral regimen for patients with genotype 1 HCV. Epclusa (brand or generic) is not recommended to be used with other products containing sofosbuvir. In the opinion of a specialist physician reviewing the data we have adopted this criterion.

2. **Life Expectancy Less Than 12 Months Due to Non-Liver Related Comorbidities.** Patients with a limited life expectancy that cannot be remediated by HCV treatment, liver transplantation, or another directed therapy do not require antiviral treatment. Patients with a short life expectancy owing to liver disease should be managed in consultation with an expert. Little evidence exists to support initiation of HCV treatment in patients with a limited life expectancy (< 12 months) owing to non-liver-related comorbid conditions. For these patients, the benefits of HCV treatment are unlikely to be realized and palliative care strategies should take precedence.

3. **Pediatric Patients (Age < 6 Years or < 17 kg).** The safety and efficacy of Epclusa (brand or generic) have not been established in pediatric patients < 6 years of age or < 17 kg.[1]

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

32. Epclusa® tablets [prescribing information]. Foster City, CA: Gilead; March 2020.
2. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. Testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org. Updated November 6, 2019. Accessed on May 29, 2020.
3. Feld JJ, Jacobson IM, Hezode C, et al; for the ASTRAL-1 Investigators. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5 and 6 infection. *N Engl J Med.* 2015;373(27):2599-2607.
4. Foster GR, Afdahl N, Roberts SK, et al; for the ASTRAL-2 and ASTRAL-3 Investigators. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. *N Engl J Med.* 2015; 31;373(27):2608-2617.
5. Curry MP, O'Leary JG, Bzowej N, et al; for the ASTRAL-4 Investigators. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. *N Engl J Med.* 2015;373(27):2618-2628.
6. Gane EJ, Shiffman ML, Etzkorn K, et al. Sofosbuvir-velpatasvir with ribavirin for 24 weeks in HCV patients previously treated with a direct-acting antiviral regimen. *Hepatology*. 2017;66(4):1083-1089.

HISTORY

Type of Revision	Summary of Changes	Review Date
New policy	New policy	06/29/2016

Selected revision	Removed requirement of a trial of another DAA for genotype 1 chronic HCV.	08/17/2016
Annual revision	Criteria for patients with genotype 1, 2, or 3 chronic HCV with prior null response, prior partial response, or relapse to Epclusa with cirrhosis or advanced cirrhosis added as an approvable condition. The condition not recommended for approval of retreatment with Epclusa in patients who were prior null or partial responders or relapsers was removed. This in now addressed in separate criteria.	06/14/2017
Annual revision	Criteria for retreatment with Epclusa in patients with genotype 1, 2, or 3 chronic HCV was removed from the policy. Criteria for patients with decompensated cirrhosis updated to address ribavirin ineligible patients. Criteria for patients with decompensated cirrhosis previously treated with Vosevi or Epclusa added to other uses with supportive evidence.	06/13/2018
DEU revision	Authorized generics to Epclusa added to targeting and applicable criteria	12/14/2018
Annual Revision	No criteria changes	06/12/2019
Selected Revision	Chronic Hepatitis C Virus (HCV) Genotype 1, 2, 3, 4, 5, or 6, No Cirrhosis or Compensated Cirrhosis (Child-Pugh A): Criteria were changed to approve for patients ≥ 6 years of age or ≥ 17 kg. Chronic Hepatitis C Virus (HCV) Genotype 1, 2, 3, 4, 5, or 6, Decompensated Cirrhosis (Child-Pugh B or C), Adults: The indication was updated to add "Adults". Chronic Hepatitis C Virus (HCV) Genotype 1, 2, 3, 4, 5, or 6, Decompensated Cirrhosis (Child-Pugh B or C), Pediatric Patients: New criteria were created to approve for 12 weeks in pediatric patients ≥ 6 years of age or ≥ 17 kg not previously treated with Epclusa when the product is prescribed by a specialist and in combination with ribavirin. Pediatric Patients (< 18 years): Criteria for this Condition Not Recommended for Approval were changed to Pediatric Patients < 6 Years or < 17 kg).	03/25/2020
Annual Revision	No criteria changes	06/17/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hepatitis C – Harvoni Prior Authorization Policy

- Harvoni® (ledipasvir/sofosbuvir tablets and oral pellets – Gilead)
- ledipasvir/sofosbuvir tablets (authorized generics to Harvoni 90 mg/400 mg tablets only – Gilead)

REVIEW DATE: 09/02/2020

OVERVIEW

Harvoni is a fixed-dose combination of ledipasvir, a hepatitis C virus (HCV) NS5A inhibitor, and sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor, indicated for[1]:

- The treatment of chronic HCV genotype 1, 4, 5, and 6 infection in adults and pediatric patients ≥ 3 years of age with or without compensated cirrhosis; and
- Adult and pediatric patients ≥ 3 years of age with genotype 1 chronic HCV with decompensated cirrhosis in combination with ribavirin; and

- Adult and pediatric patients ≥ 3 years of age with genotype 1 or 4 chronic HCV who are liver transplant recipients with or without compensated cirrhosis, in combination with ribavirin.

Dosing

In adults, the recommended dosage of Harvoni is one tablet taken orally once daily with or without food.[1] The recommended dose of Harvoni tablets or pellets in pediatric patients ≥ 3 years of age is based on weight. The Harvoni pellets can be taken in pediatric patients who cannot swallow the tablet formulation. Table 1 below provides the recommended duration of therapy with Harvoni. The Harvoni authorized generic is only available as the 90 mg/400 mg strength tablet; Harvoni is additionally available as a lower strength tablet (45 mg/200 mg) as well as oral pellets (45 mg/200 mg and 33.75 mg/150 mg).

Table 1. Recommended Treatment Duration for Harvoni in Patients ≥ 3 Years of Age with Chronic HCV Genotype 1, 4, 5, or 6.[1]

Patient Population	Duration of Treatment
Genotype 1 – Treatment-naïve with or without compensated (Child Pugh A) cirrhosis	Harvoni 12 weeks*
Genotype 1 – Treatment-experienced** without cirrhosis	Harvoni 12 weeks
Genotype 1 – Treatment-experienced** with compensated (Child Pugh A) cirrhosis	Harvoni 24 weeks†
Genotype 1 – Treatment-naïve and treatment-experienced** with decompensated (Child-Pugh B or C) cirrhosis.	Harvoni + ribavirin‡ 12 weeks
Genotype 1 or 4 – Transplant recipients without cirrhosis, or with compensated (Child-Pugh A) cirrhosis	Harvoni + ribavirin§ 12 weeks
Genotype 4, 5, or 6 – Treatment-naïve and treatment-experienced**, with or without compensated (Child-Pugh A) cirrhosis	Harvoni 12 weeks

Hepatitis C virus – Hepatitis C virus; * Harvoni for 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pretreatment HCV RNA < 6 million IU/mL; ** Treatment-experienced patients who have failed treatment with either peginterferon alfa + ribavirin or a hepatitis C virus protease inhibitor + peginterferon + ribavirin; † Harvoni for 12 weeks can be considered in treatment-experienced patients with cirrhosis who are eligible for ribavirin. The daily dose of ribavirin is weight-based (1,000 mg for patients < 75 kg and 1,200 mg for those ≥ 75 kg) administered in two divided doses. ‡ In patients with decompensated cirrhosis, the starting dosage of ribavirin is 600 mg and can be titrated up to 1,000 mg for patients <75 kg and 1,200 mg for those ≥75 kg in two divided doses with food. If the starting dosage of ribavirin is not well tolerated, the dosage should be reduced as clinically indicated based on hemoglobin levels. § The daily dosage of ribavirin is weight-based (1,000 mg for patients < 75 kg and 1,200 mg for those ≥ 75 kg) administered orally in two divided doses with food.

Guidelines

For the most up-to-date guideline information always refer to the American Association for the Study of Liver Diseases (AASLD) guidelines. Harvoni is recommended in the circumstances outlined in Table 2.

Table 2. AASLD Recommendations for Harvoni.[2]

DAA	Duration	FDA Approved (Y/N)	AASLD Level of Evidence
Genotype 1, 4, 5, and 6 Chronic HCV Treatment-Naïve Adults – Recommended			
Harvoni	12 weeks (± compensated cirrhosis)	Y	Class I, Level A Class IIa, Level B (Genotype 4 compensated cirrhosis, Genotype 5/6 ± compensated cirrhosis)
Harvoni	8 weeks (HIV-uninfected, HCV RNA < 6 million IU/mL, no cirrhosis)	Y	Class I, Level B
Genotype 1, 4, 5, and 6 Chronic HCV Pegylated Interferon/Ribavirin Treatment-Experienced Adults – Recommended			
Harvoni	12 weeks (no cirrhosis)	Y	Class I, Level A (Genotype 1) Class IIa, Level B (Genotype 4, 5, 6)
Harvoni	12 weeks (compensated cirrhosis)	Y	Class IIa, Level B (Genotype 5/6)
Genotype 1 and 4 Chronic HCV Pegylated Interferon/Ribavirin Treatment-Experienced Adults – Alternative			
Harvoni + WBR	12 weeks (compensated cirrhosis)	Y (Genotype 1) N (Genotype 4)	Class I, Level A (Genotype 1) Class IIa, Level B (Genotype 4)
Genotype 1 Chronic HCV NS3/4A + Pegylated Interferon/Ribavirin Treatment-Experienced Adults – Recommended			
Harvoni	12 weeks (no cirrhosis)	Y	Class I, Level A
Genotype 1 Chronic HCV NS3/4A + Pegylated Interferon/Ribavirin Treatment-Experienced Adults – Alternative			
Harvoni + WBR	12 weeks (compensated cirrhosis)	Y	Class I, Level A
Genotype 1 Chronic HCV Non-NS5A Sovaldi-Containing Treatment-Experienced Adults – Alternative			
Harvoni + WBR	12 weeks (no cirrhosis)	N	Class IIa, Level B
Genotype 1, 4, 5, or 6 Chronic HCV, Decompensated Cirrhosis Adults Ribavirin Eligible – Recommended			
Harvoni + ribavirin	12 weeks	Y	Class I, Level A
Genotype 1, 4, 5, or 6 Chronic HCV, Decompensated Cirrhosis Adults Ribavirin Ineligible – Recommended			
Harvoni	24 weeks	N	Class I, Level A
Genotype 1, 4, 5, or 6 Chronic HCV, Decompensated Cirrhosis Adults Prior Sovaldi-Based Failure Only – Recommended			
Harvoni + ribavirin	24 weeks	N	Class II, Level C
Genotype 1, 4, 5, or 6 Recurrent HCV Post-Liver Transplant, No Cirrhosis, Treatment-Naïve or Treatment-Experienced – Recommended			
Harvoni + WBR	12 weeks	Y	Class I, Level B
Genotype 1, 4, 5, or 6 Recurrent HCV Post-Liver Transplant, Compensated Cirrhosis, Treatment-Naïve or Treatment-Experienced – Recommended			
Harvoni + WBR	12 weeks	Y	Class I, Level A
Genotype 1, 4, 5, or 6 Recurrent HCV Post-Liver Transplant, Decompensated Cirrhosis, Treatment-Naïve or Treatment-Experienced – Recommended			
Harvoni + ribavirin	12 to 24 weeks	Y	Class I, Level B
Genotype 1, 4, 5, or 6 Organ Recipients from HCV RNA-Positive Donors, Adults – Recommended			
Harvoni	12 weeks	N	Class I, Level C

Table 2 (continued). AASLD Recommendations for Harvoni.[2]

DAA	Duration	FDA Approved (Y/N)	AASLD Level of Evidence
Genotype 1, 4, 5, or 6 Kidney Transplant Treatment-Naïve or DAA-Experienced ± Compensated Cirrhosis, Adults – Recommended			
Harvoni	12 weeks	N	Class I, Level A
Genotype 1, 4, 5, or 6 Treatment-Naïve Adolescents ≥ 12 years or ≥ 45 kg, ± Compensated Cirrhosis – Recommended			
Harvoni	12 weeks	Y	Class I, Level B
Genotype 1, 4, 5, or 6 Treatment-Experienced Adolescents ≥ 12 years or ≥ 45 kg, ± Compensated Cirrhosis – Recommended			
Harvoni	24 weeks (GT1 compensated cirrhosis)	Y	Class I, Level B
Harvoni	12 weeks (GT 4, 5, or 6 ± compensated cirrhosis)	Y	Class I, Level B

AASLD – American Association for the Study of Liver Diseases; DAA – Direct-acting antiviral; Y – Yes; N – No; HCV – Hepatitis C virus; HIV – Human immunodeficiency virus.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Harvoni (brand or generic). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Harvoni (brand or generic) as well as the monitoring required for adverse events and long-term efficacy, approval requires Harvoni (brand or generic) to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Harvoni (brand or generic) is recommended in those who meet the following criteria:

FDA-Approved Indications

52. Chronic Hepatitis C Virus (HCV) Genotype 1. Approve for the duration noted if the patient meets all of the following criteria (A, B, and C):

A) Patient is ≥ 3 years of age; AND

B) Patient meets ONE of the following criteria (i, ii or iii):

i. Approve for 8 weeks if the patient meets all of the following criteria (a, b, c, d, and e):

a) Patient is treatment-naïve; AND

b) Patient does not have cirrhosis; AND

c) Patient does not have human immunodeficiency virus (HIV)[2] (patients with HIV should be reviewed the same as patients without HIV using *Criteria ii or iii below*); AND

d) Patient is not awaiting liver transplantation (patients awaiting liver transplantation should be reviewed using *Criteria ii or iii below*); AND

e) Baseline hepatitis C virus (HCV) RNA is < 6 million IU/mL; OR

ii. Approve for 12 weeks if the patient meets ONE the following criteria (a, b, or c):

a) Patient is treatment-naïve AND does not meet criterion *Bi* above; OR

Note: Treatment-naïve includes patients with or without HIV who are treatment-naïve with compensated [Child-Pugh A] cirrhosis regardless of baseline HCV RNA, or treatment-naïve patients with or without HIV without cirrhosis and baseline HCV RNA ≥ 6 million IU/mL. This would also include treatment-naïve patients awaiting transplant with compensated [Child-Pugh A] cirrhosis regardless of baseline HCV RNA or treatment-naïve patients awaiting transplant without cirrhosis and baseline HCV RNA ≥ 6 million IU/mL).

b) Patient has previously been treated for hepatitis C virus (HCV) and does not have cirrhosis; OR

Note: For patients with compensated cirrhosis [Child-Pugh A] see criterion *Biii* below, for patients with decompensated cirrhosis [Child-Pugh B or C] see criterion *Biic* below.

c) Patient is treatment-naïve or has previously been treated for hepatitis C virus (HCV) and meets all of the following criteria ([1], [2], and [3]):

(1) Patient has decompensated (Child-Pugh B or C) cirrhosis; AND

(2) Patient is ribavirin eligible; AND

Note: For ribavirin ineligible patients with decompensated cirrhosis, see criterion *Biiib* below

(3) Harvoni (brand or generic) will be prescribed in combination with ribavirin; OR

iii. Approve for 24 weeks in patients who meet ONE of the following (a or b):

(1) Patient has previously been treated for hepatitis C virus (HCV) and has compensated (Child-Pugh A) cirrhosis; OR

(2) Patient is treatment-naïve or has previously been treated for hepatitis C virus (HCV) and the patient meets both of the following criteria ([1] and [2]):

a. Patient has decompensated (Child-Pugh B or C) cirrhosis; AND

b. Patient is ribavirin ineligible, according to the prescriber; AND

C) Harvoni (brand or generic) is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

2. **Chronic Hepatitis C Virus (HCV) – Genotype 4, 5, OR 6.** Approve for 12 weeks if the patient meets the following criteria (A and B):
   - **A)** Patient is ≥ 3 years of age; AND
   - **B)** Harvoni (brand or generic) is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

3. **Recurrent Hepatitis C Virus (HCV) Post-Liver Transplantation, Genotypes 1 OR 4.** Approve for 12 weeks if the patient meets the following criteria (A, B, C and D):
   - **A)** Patient is ≥ 3 years of age; AND
   - **B)** Patient has recurrent hepatitis C virus (HCV) after a liver transplantation; AND
   - **C)** Harvoni (brand or generic) will be prescribed in combination with ribavirin; AND
   - **D)** Harvoni (brand or generic) is prescribed by or in consultation with one of the following prescribers who is affiliated with a transplant center[2]: a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

Other Uses with Supportive Evidence

4. **Recurrent Hepatitis C Virus (HCV) Post-Liver Transplantation, Genotypes 5 OR 6**. Approve for 12 weeks if the patient meets the following criteria (A, B, C and D):
   - **C)** Patient is ≥ 18 years of age; AND
   - **D)** Patient has recurrent hepatitis C virus (HCV) after a liver transplantation; AND
   - **E)** Harvoni (brand or generic) will be prescribed in combination with ribavirin; AND
   - **F)** Harvoni (brand or generic) is prescribed by or in consultation with one of the following prescribers who is affiliated with a transplant center[2]: a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

5. **Hepatitis C Virus (HCV) Kidney Transplant Recipients, Genotype 1 or 4.** Approve for 12 weeks if the patient meets the following criteria (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient is a kidney transplant recipient with hepatitis C virus (HCV); AND
   - **C)** Harvoni (brand or generic) is prescribed by or in consultation with one of the following prescribers who is affiliated with a transplant center[2]: a gastroenterologist, hepatologist, infectious diseases physician, nephrologist, liver transplant physician, or a renal transplant physician.

6. **Patient Has Been Started on Harvoni (brand or generic).** Approve Harvoni (brand or generic) for an indication or condition addressed as an approval in the Recommended Authorization Criteria section

(FDA-Approved Indications or Other Uses with Supportive Evidence). Approve the duration described above to complete a course of therapy (e.g., a patient who should receive 12 weeks, and has received 3 weeks should be approved for 9 weeks to complete their 12-week course).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Harvoni is not recommended in the following situations:

67. **Hepatitis C Virus (HCV) [any genotype], Combination with Any Other Direct-Acting Antivirals (DAAs) Not Including Ribavirin.** Harvoni (brand or generic) provides a complete antiviral regimen for patients with genotype 1 HCV. Harvoni (brand or generic) is not recommended to be used with other products containing sofosbuvir.

68. **Life Expectancy Less Than 12 Months Due to Non-Liver Related Comorbidities.** Patients with limited life expectancy for whom HCV therapy would not improve symptoms or prognosis do not require treatment.[2] According to AASLD guidance, the panel recommends treatment for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. For these patients, the benefits of HCV treatment are unlikely to be realized, and palliative care strategies should take precedence.

69. **Pediatric Patients (Age < 3 years).** The safety and efficacy of Harvoni (brand or generic) have not been established in pediatric patients < 3 years of age.[1]

70. **Retreatment with Harvoni (brand or generic) in Patients Who Have Previously Received Harvoni (brand or generic) (e.g., retreatment in prior null responders, prior partial responders, prior relapse patients, patients who have not completed a course of therapy due to an adverse reaction or for other reasons)**. There are other direct-acting antivirals indicated for patients who have previously been treated with Harvoni (brand or generic).

71. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

33. Harvoni® tablets and oral pellets [prescribing information]. Foster City, CA: Gilead; March 2020.
2. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. Testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org. Updated November 6, 2019. Accessed on August 18, 2020.
3. Charlton M, Everson GT, Flamm SL, et al; for the SOLAR-1 Investigators. *Gastroenterology*. 2015;149:649-659.
4. Naggie, Cooper C, Saag M, et al; for the ION-4 Investigators. Ledipasvir and sofosbuvir for HCV in patients coinfected with HIV-1. *N Engl J Med.* 2015;373:705-713.
5. Bourliere M, Bronowicki JP, de Ledinghen V, et al. Ledipasvir+sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomized, double-blind, phase 2 trial (SIRIUS). *Lancet Infect Dis.* 2015; 15:397-404.
6. Balistreri WF, Murray KF, Rosenthal P, et al. The safety and effectiveness of ledipasvir-sofosbuvir in adolescents 12 to 17 years old with hepatitis C virus genotype 1 infection. *Hepatology*. 2017;66(2):371-378.
7. Data on file. Gilead, Foster City CA. April 10, 2017.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	Added criteria for patients with genotype 1 who are ribavirin ineligible.	10/03/2018
Update	12/14/2018: Authorized generics to Harvoni added to targeting and applicable criteria	NA
Annual revision	Chronic Hepatitis C Virus (HCV) Genotype 1, Adults: "Adults" was removed, age indication revised to include patients ≥ 3 years of age.	09/04/2019

	Chronic Hepatitis C Virus (HCV) Genotype 1, Pediatric Patients: Criteria removed, these patients are addressed under Chronic Hepatitis C Virus (HCV) Genotype 1 criteria. Chronic Hepatitis C Virus (HCV) – Genotype 4, 5, OR 6, Adults: "Adults" was removed, age indication revised to include patients ≥ 3 years of age. Chronic Hepatitis C Virus (HCV) – Genotype 4, 5, OR 6, Pediatric Patients: Criteria removed these patients are addressed under Chronic Hepatitis C Virus (HCV) Genotype 4, 5, OR 6 criteria. Recurrent Hepatitis C Virus (HCV) Post-Liver Transplantation, Genotypes 1 OR 4, Adults: Removed "adults", age indication revised to include patients ≥ 3 years of age. In conditions not recommended for approval: Pediatric Patients (Age < 12 years or < 35 kg): Age indication revised to < 3 years, weight removed.	
Annual revision	**Chronic Hepatitis C Virus (HCV) Genotype 1:** For patients who are treatment-naïve or previously treated for hepatitis C virus (HCV) with decompensated (Child-Pugh B or C) cirrhosis who are ribavirin ineligible; "according to the prescribing physician" was changed to "according to the prescriber".	09/02/2020

NA – Not applicable.

PRIOR AUTHORIZATION POLICY

POLICY: Hepatitis C – Mavyret Prior Authorization Policy

- Mavyret™ (glecaprevir/pibrentasvir tablets – AbbVie)

REVIEW DATE: 08/19/2020

OVERVIEW

Mavyret, a direct-acting antiviral, is indicated for the treatment of adult and pediatric patients ≥ 12 years of age or ≥ 45 kg with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A).[1] Mavyret is also indicated for the treatment of adult and pediatric patients ≥ 12 years of age or ≥ 45 kg with HCV genotype 1 infection who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both.[1] Mavyret contains glecaprevir, a new pangenotypic NS3/4A protease inhibitor and pibrentasvir, a new pangenotypic NS5A inhibitor.

Dosing

The recommended dose of Mavyret is three tablets (total daily dose: glecaprevir 300 mg and pibrentasvir 120 mg) taken once daily with food. No dosage adjustments are required for patients with human immunodeficiency virus (HIV) co-infection and/or chronic kidney disease, including dialysis. The duration of therapy is based on prior treatment experience, genotype, and the presence or absence of cirrhosis (see Table 1). Mavyret is recommended for 12 weeks in adults and pediatric patients ≥ 12 years of age or ≥ 45 kg liver or kidney transplant recipients. Similar to non-transplant recipients, a 16-week treatment duration is recommended in genotype 1-infected patients who are NS5A inhibitor-experienced without prior treatment with an NS3/4A protease inhibitor or in genotype 3-infected patients who are treatment experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or Sovaldi® (sofosbuvir tablets).

Table 1. Recommended Duration for Treatment-Naïve Patients.[1]

HCV Genotype	Treatment Duration	
	No Cirrhosis	Compensated Cirrhosis (Child-Pugh A)
1, 2, 3, 4, 5, or 6	8 weeks	8 weeks

HCV – Hepatitis C virus.

Table 2. Recommended Duration for Treatment-Experienced Patients.[1]

HCV Genotype	Prior Treatment Experience	Duration

		Without Cirrhosis	With Compensated Cirrhosis
1, 2, 4, 5, 6	PRS	8 weeks	12 weeks
3	PRS	16 weeks	16 weeks
1	NS3/4 PI[1] (NS5A-naïve)	12 weeks	12 weeks
	NS5A inhibitor[2] (NS3/4 PI-naïve)[†]	16 weeks	16 weeks

HCV – Hepatitis C virus; PRS – Prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin, and/or Sovaldi® (sofosbuvir tablets), but no prior treatment experience with an HCV NS3/4A protease inhibitor (PI) or NS5A inhibitor; PI – Protease inhibitor; [1] Regimens containing Olysio® (simeprevir capsules) and Sovaldi, or Olysio, Victrelis® (boceprevir capsules), or Incivek® (telaprevir tablets) with interferon or pegylated interferon and ribavirin were studied; [2] Regimens containing Harvoni® (ledipasvir/sofosbuvir tablets) or Daklinza® (daclatasvir tablets) + pegylated interferon + ribavirin [unapproved regimen] were studied.

Guidelines

The American Association for the Study of Liver Diseases (AASLD)/ Infectious Diseases Society of America (IDSA) recommendations related to Mavyret are summarized below in Table 3. For the most up-to-date information always refer to the guidelines. In treatment-naïve adults without cirrhosis the recommended regimens are Mavyret for 8 weeks or Epclusa for 12 weeks. In treatment-naïve adults with compensated cirrhosis, the recommended regimens are Mavyret for 8 weeks (genotypes 1 through 6) or Epclusa for 12 weeks (genotypes 1, 2, 4, 5, or 6; patients with genotype 3 require baseline NS5A resistance-associated substitution testing and those without Y93H can be treated with 12 weeks of Epclusa). Additional genotype-specific and/or special circumstance-specific recommendations are also provided (Table 3).

Table 3. AASLD Recommendations for Mavyret.[7]

DAA	Duration	FDA Approved (Y/N)	AASLD Level of Evidence
Chronic HCV – Treatment-Naïve – Recommended			
Genotype 1, 2, 3, 4, 5, 6 – No Cirrhosis			
Mavyret	8 weeks	Y	Class I, Level A
Genotype 1, 3 Compensated Cirrhosis			
Mavyret	8 weeks	Y	Class I, Level B
Genotype 2, 4, 5, 6 Compensated Cirrhosis			
Mavyret	12 weeks	Y	Class I, Level B
Chronic HCV – Treatment-Experienced			
Peglyated Interferon/Ribavirin			
Genotype 1, 2, 4, 5, 6 – Recommended			
Mavyret	8 weeks (no cirrhosis) 12 weeks (compensated cirrhosis)	Y Y	Class I, Level A (Class IIa, Level B for genotype 5) Class I, Level B (Class IIa, Level B for genotype 4)
Genotype 3 – Alternative			
Mavyret	16 weeks (± compensated cirrhosis)	Y	Class IIa, Level B
NS3/4A (Incivek, Victrelis, Olysio + Pegylated Interferon/Ribavirin			
Genotype 1 – Recommended			
Mavyret	12 weeks (± compensated cirrhosis)	Y	Class IIa, Level B
Non-NS5A Sovaldi-Containing Regimen			
Genotype 1 – Alternative			
Mavyret	16 weeks (± compensated cirrhosis NOT NS3/4A experienced)	Y	Class IIa, Level B
Sovaldi + WBR			
Genotype 2 – Recommended			
Mavyret	12 weeks (± compensated cirrhosis)	Y	Class IIb, Level B
Genotype 3 – Recommended			
Mavyret	16 weeks (± compensated cirrhosis)	N	Class IIb, Level B
Recurrent HCV Post-Liver Transplant –Treatment-Naïve or Treatment-Experienced			
Genotype 1, 2, 3, 4, 5, 6 – Recommended			
Mavyret	12 weeks (± compensated cirrhosis)	N	Class I, Level B (no cirrhosis) Class 1, Level C (compensated cirrhosis)
Organ Recipients from HCV RNA-Positive Donors			
Genotype 1, 2, 3, 4, 5, 6 – Recommended			
Mavyret	12 weeks	N	Class I, Level C

Stage 4 or 5 CKD (eGFR < 30 mL/min) or ESRD and Chronic HCV			
Genotype 1, 2, 3, 4, 5, 6 – Recommended			
Mavyret	8 to 16 weeks	Y	Class I, Level A

Table 3 (continued). AASLD Recommendations for Mavyret.[7]

DAA	Duration	FDA Approved (Y/N)	AASLD Level of Evidence
Kidney Transplant with HCV Treatment-Naïve or –Experienced ± Compensated Cirrhosis			
Genotype 1, 2, 3, 4, 5, 6 – Recommended			
Mavyret	12 weeks	Y	Class I, Level A (no cirrhosis) Class IIa, Level C (compensated cirrhosis)
Pediatric Patients			
Genotype 1, 2, 3, 4, 5, 6 – Treatment-Naïve Adolescents ≥ 12 years or ≥ 45 kg, ± Compensated Cirrhosis – Recommended			
Mavyret	8 weeks	Y	Class I, Level B
Genotype 1, 2, 3, 4, 5, 6 – Treatment-Experienced Adolescents ≥ 12 years or ≥ 45 kg, ± Compensated Cirrhosis – Recommended			
Mavyret	8 weeks (GT 1, 2, 4, 5, or 6 without cirrhosis)	Y	Class I, Level B
	12 weeks (GT 1, 2, 4, 5, or 6 compensated cirrhosis)	Y	Class I Level B
	16 weeks (GT 3 ± compensated cirrhosis)	Y	Class I, Level B
	16 weeks (GT1 ± compensated cirrhosis)	Y	Class I, Level B
	12 weeks (GT1 without cirrhosis)	Y	Class I, Level B

AASLD – American Association for the Study of Liver Diseases; DAA – Direct-acting antiviral; Y – Yes; N – No; HCV – Hepatitis C virus; WBR – Weight-based ribavirin; CKD – Chronic kidney disease; ESKD – End-stage kidney disease.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Mavyret. See criteria for approval durations. Because of the specialized skills required for evaluation and diagnosis of patients treated with Mavyret as well as the monitoring required for adverse events and efficacy, approval requires Mavyret to be prescribed by or in consultation with a physician who specialized in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mavyret is recommended in those who meet the following criteria:

FDA-Approved Indications

53. Chronic Hepatitis C Virus (HCV) Genotype 1, 2, 3, 4, 5, or 6, Treatment-Naïve. Approve for 8 weeks if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 12 years of age OR ≥ 45 kg; AND
- **B)** Patient is HCV treatment-naïve (the patient has not previously received treatment for their chronic HCV infection); AND
- **C)** Mavyret is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

54. Chronic Hepatitis C Virus (HCV), Genotype 1, Treatment-Experienced. Approve for the duration noted if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 12 years of age OR ≥ 45 kg; AND
- **B)** Patient meets ONE of the following conditions (i, ii, iii, or iv):

  NS5A-Experienced, NS3/4-Naïve
  - **i.** Approve for 16 weeks if the patient meets both of the following criteria (a, b, and c):
    - **a)** The patient does not have cirrhosis or has compensated cirrhosis (Child-Pugh A); AND

b) Patient had a prior null response, prior partial response, or had relapse after prior treatment with one of the following NS5A-inhibitor containing products: Daklinza (daclatasvir tablets), Epclusa (sofosbuvir/velpatasvir brand or generic), Harvoni (ledipasvir/sofosbuvir tablets/oral pellets; brand or generic); AND

c) Patient has not previously been treated with one of the following NS3/4A inhibitor or NS3/4A inhibitor-containing products: Olysio (simeprevir capsules), Victrelis (boceprevir capsules), or Incivek (telaprevir tablets), Technivie (ombitasvir/paritaprevir/ritonavir tablets), Viekira Pak (ombitasvir/paritaprevir/ritonavir tablets; dasabuvir tablets, co-packaged), Viekira XR (dasabuvir/ombitasvir/paritaprevir/ritonavir extended-release tablets), Vosevi (sofosbuvir/velpatasvir/voxilaprevir); or Zepatier (elbasvir/grazoprevir tablets); OR

NS3/4-Experienced, NS5A-Naïve

ii. Approve for 12 weeks if the patient meets both of the following criteria (a, b, and c):

a) Patient does not have cirrhosis or has compensated cirrhosis (Child-Pugh A).

b) Patient has not previously been treated with one of the following NS5A-inhibitor-containing products: Daklinza (daclatasvir tablets), Epclusa (sofosbuvir/velpatasvir brand or generic), Harvoni (ledipasvir/sofosbuvir tablets/oral pellets; brand or generic), Technivie (ombitasvir/paritaprevir/ritonavir tablets), Viekira Pak (ombitasvir/paritaprevir/ritonavir tablets; dasabuvir tablets, co-packaged), Viekira XR (dasabuvir/ombitasvir/paritaprevir/ritonavir extended-release tablets), Vosevi (sofosbuvir/velpatasvir/voxilaprevir), or Zepatier (elbasvir/grazoprevir tablets); AND

c) Patient had a prior null response, prior partial response, or had relapse after prior treatment with one of the following NS3/4A inhibitor or NS3/4A inhibitor-containing products: Olysio (simeprevir capsules), Victrelis (boceprevir capsules), or Incivek (telaprevir tablets); OR

Pegylated Interferon/Interferon, Ribavirin, Sovaldi-Experienced

iii. Approve for 8 weeks if the patient meets both of the following criteria (a and b):

a) Patient does not have cirrhosis; AND

b) Patient had a prior null response, prior partial response, or had relapse after prior treatment with one of the following regimens: interferon ± ribavirin, pegylated interferon ± ribavirin, Sovaldi (sofosbuvir tablets/oral pellets) + ribavirin, Sovaldi + pegylated interferon + ribavirin; AND

iv. Approve for 12 weeks if the patient meets both of the following criteria (a and b):

a) Patient has compensated cirrhosis (Child-Pugh A); AND

b) Patient had a prior null response, prior partial response, or had relapse after prior treatment with one of the following regimens: interferon ± ribavirin, pegylated interferon ± ribavirin, Sovaldi (sofosbuvir tablets/oral pellets) + ribavirin, Sovaldi + pegylated interferon + ribavirin; AND

C) Mavyret is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

55. Chronic Hepatitis C Virus (HCV), Genotype 2, 4, 5, or 6, Treatment-Experienced. Approve for the duration noted if the patient meets the following criteria (A, B, C, and D):

A) Patient is ≥ 12 years of age OR ≥ 45 kg; AND

B) Patient meets ONE of the following (i or ii):

i. Approve for 8 weeks if the patient meets both of the following criteria (a and b):

a) Patient does not have cirrhosis; AND

b) Patient had a prior null response, prior partial response, or had relapse after prior treatment with one of the following regimens: interferon ± ribavirin, pegylated interferon ± ribavirin, Sovaldi (sofosbuvir tablets/oral pellets)+ ribavirin, Sovaldi + pegylated interferon + ribavirin; OR

ii. Approve for 12 weeks if the patient meets both of the following criteria a and b):

a) Patient has compensated cirrhosis (Child-Pugh A); AND

b) Patient had a prior null response, prior partial response, or had relapse after prior treatment with one of the following regimens: interferon ± ribavirin, pegylated interferon ± ribavirin, Sovaldi (sofosbuvir tablets/oral pellets) + ribavirin, Sovaldi + pegylated interferon + ribavirin; AND

C) Mavyret is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

56. Chronic Hepatitis C Virus (HCV), Genotype 3, Treatment-Experienced. Approve for 16 weeks if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is 12 years of age OR ≥ 45 kg; AND
- **B)** Patient does not have cirrhosis or has compensated cirrhosis (Child-Pugh A); AND
- **C)** Patient had a prior null response, prior partial response, or had relapse after prior treatment with one of the following regimens: interferon ± ribavirin, pegylated interferon ± ribavirin, Sovaldi (sofosbuvir tablets/oral pellets) + ribavirin, Sovaldi + pegylated interferon + ribavirin; AND
- **D)** Mavyret is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

57. Hepatitis C Virus (HCV) Kidney or Liver Transplant Recipients, Genotype 1, 2, 3, 4, 5, OR 6. Approve for the duration noted if the patient meets all of the following criteria (A, B, C and D):
- **A)** Patient is 12 years of age OR ≥ 45 kg; AND
- **B)** Patient is a kidney or liver transplant recipient with hepatitis C virus (HCV); AND
- **C)** Patient meets one of the following conditions (i, ii, or iii):
  - **i.** Patient has genotype 2, 4, 5, or 6 HCV: Approve for **12 weeks**;
  - **ii.** Patient has genotype 1 HCV: Approve for the duration below (a or b):

    NS5A-Experienced, NS3/4-Naïve
    - **a)** Approve for 16 weeks if the patient meets both of the following criteria (1 and 2):
      - **(1)** Patient had a prior null response, prior partial response, or had relapse after prior treatment with one of the following NS5A-inhibitor containing products: Daklinza (daclatasvir tablets), Epclusa (sofosbuvir/velpatasvir brand or generic) Harvoni (ledipasvir/sofosbuvir tablets/oral pellets; brand or generic); AND
      - **(2)** Patient has not previously been treated with one of the following NS3/4A inhibitor or NS3/4A inhibitor-containing products: Olysio (simeprevir capsules), Victrelis (boceprevir capsules), or Incivek (telaprevir tablets), Technivie (ombitasvir/paritaprevir/ritonavir tablets), Viekira Pak (ombitasvir/paritaprevir/ritonavir tablets; dasabuvir tablets, co-packaged), Viekira XR (dasabuvir/ombitasvir/paritaprevir/ritonavir extended-release tablets), Vosevi (sofosbuvir/velpatasvir/voxilaprevir); or Zepatier (elbasvir/grazoprevir tablets). OR
    - **b)** Approve for 12 weeks for all other patients with genotype 1 HCV; OR
  - **iii.** Patient has genotype 3 HCV: Approve for the duration below (a or b):
    - **a)** Approve for 16 weeks if the patient meets the following criteria (1):
      - **(1)** Patient had a prior null response, prior partial response, or had relapse after prior treatment with one of the following regimens: interferon ± ribavirin, pegylated interferon ± ribavirin, Sovaldi (sofosbuvir tablets/oral pellets) + ribavirin, Sovaldi + pegylated interferon + ribavirin**;** OR
    - **b)** Approve for 12 weeks for all other patients with genotype chronic HCV; AND
- **D)** Mavyret is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

Other Uses with Supportive Evidence

58. Recurrent Hepatitis C Virus (HCV) Post-Liver Transplantation, Genotype 1, 2, 3, 4, 5, OR 6. Approve for 12 weeks in patients who meet the following criteria (A, B, and C):
- **A)** Patient is ≥ 12 years of age OR ≥ 45 kg; AND
- **B)** Patient has recurrent hepatitis C virus (HCV) after a liver transplantation; AND

C) Mavyret is prescribed by or in consultation with one of the following prescribers who is affiliated with a transplant center: a gastroenterologist, hepatologist, infectious diseases physician, or liver transplant physician.

59. Patient Has Been Started on Mavyret. Approve for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications or Other Uses with Supportive Evidence). Approve the duration described above to complete a course therapy (e.g., a patient who should receive 12 weeks, and has received 3 weeks should be approved for 9 weeks to complete their 12-week course).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Mavyret is not recommended in the following situations:

72. Hepatitis C Virus (HCV) Child-Pugh Class B or C Liver Disease (Moderate or Severe Hepatic Impairment). Mavyret is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C).

73. Hepatitis C Virus (HCV) [any genotype], Combination with Any Other Direct-Acting Antivirals. Mavyret provides a complete antiviral regimen.

74. Life Expectancy Less Than 12 Months Due to Non-Liver Related Comorbidities. Patients with a limited life expectancy that cannot be remediated by HCV treatment, liver transplantation, or another directed therapy do not require antiviral treatment.[2] Patients with a short life expectancy owing to liver disease should be managed in consultation with an expert. Little evidence exists to support initiation of HCV treatment in patients with a limited life expectancy (< 12 months) owing to non-liver-related comorbid conditions. For these patients, the benefits of HCV treatment are unlikely to be realized and palliative care strategies should take precedence.

75. Pediatric Patients (Age < 12 Years or < 45 kg). The safety and efficacy of Mavyret have not been established in pediatric patients < 12 years of age or < 45 kg.[1]

76. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

221. Mavyret™ tablets [prescribing information]. North Chicago, IL: AbbVie; May 2020.
222. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. Testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org. Updated November 6, 2019. Accessed on August 11, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	Chronic Hepatitis C Virus, Genotype 1, Treatment-Experienced: Epclusa was added to the list of NS5A inhibitors in NS5A-experienced, NS3/4-naïve adults. HCV Post Kidney Transplant Genotype 1, 2, 3, 4, 5, or 6: -Criteria were added to include post-liver transplant HCV patients. -For patients with genotype 1 who are NS5A-experienced NS3/4A naïve, criteria were added to approve for 16 weeks. -For patients with genotype 3 who are pegylated interferon/ribavirin/Sovaldi-experienced, criteria were added to approve for 16 weeks. All other patients are approved for 12 weeks. -This indication was moved from other uses with supportive evidence to FDA-Approved uses.	08/15/2018
Update	Addition of generics to Epclusa and Harvoni	12/14/2018
Selected revision	1. Chronic Hepatitis C Virus (HCV) Genotype 1, 2, 3, 4, 5, or 6, Treatment-Naïve: Added criteria for pediatric patients ≥ 12 years of age or ≥ 45 kg, previously approved for patients ≥ 18 years of age. 2. Chronic Hepatitis C Virus (HCV), Genotype 1, Treatment-Experienced: Added criteria for pediatric patients ≥ 12 years of age or ≥ 45 kg, previously approved for patients ≥ 18 years of age. 3. Chronic Hepatitis C Virus (HCV), Genotype 2, 4, 5, or 6, Treatment-Experienced: Added criteria for pediatric patients ≥ 12 years of age or ≥ 45 kg, previously approved for patients ≥ 18 years of age. 4. Chronic Hepatitis C Virus (HCV), Genotype 3, Treatment-Experienced: Added criteria for pediatric patients ≥ 12 years of age or ≥ 45 kg, previously approved for patients ≥ 18 years of age. 5. Hepatitis C Virus (HCV) Kidney or Liver Transplant Recipients, Genotype 1, 2, 3, 4, 5, OR 6: Added criteria for pediatric patients ≥ 12 years of age or ≥ 45 kg, previously approved for patients ≥ 18 years of age. 6. Recurrent Hepatitis C Virus (HCV) Post-Liver Transplantation, Genotype 1, 2, 3, 4, 5, OR 6: Added criteria for pediatric patients ≥ 12 years of age or ≥ 45 kg, previously approved for patients ≥ 18 years of age. 7. Recurrent Hepatitis C Virus (HCV) Post-Liver Transplantation, Genotype 1, 2, 3, 4, 5, OR 6: Added criteria for pediatric patients ≥ 12 years of age or ≥ 45 kg, previously approved for patients ≥ 18 years of age. 8. Pediatric Patients (Age < 18 Years of Age): This exclusion criterion was updated to < 12 years of age or < 45 kg.	05/08/2019
Annual revision	No criteria changes	08/28/2019
Selected revision	Chronic Hepatitis C Virus (HCV) Genotype 1, 2, 3, 4, 5, or 6, Treatment-Naïve: Approval duration was changed to 8 weeks for all patients. Hepatitis C Virus (HCV) Child-Pugh Class C Liver Disease (Severe Hepatic Impairment): This Condition Not Recommended for Approval was expanded to include patients with Child-Pugh B Liver Disease (Moderate Hepatic Impairment).	10/02/2019

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	Chronic Hepatitis C Virus (HCV), Genotype 1, Treatment-Experienced: Harvoni oral pellets were added to criteria for NS5A-Experienced, NS3/4-Naïve and NS3/4-Experienced/NS5A-Naïve. For pegylated interferon/interferon, ribavirin, Sovaldi-experienced patients, Sovaldi was clarified to include tablets and oral pellets. Chronic Hepatitis C Virus (HCV), Genotype 2, 4, 5, or 6, Treatment-Experienced. Sovaldi was clarified to include tablets and oral pellets. Chronic Hepatitis C Virus (HCV), Genotype 3, Treatment-Experienced. Sovaldi was clarified to include tablets and oral pellets. Hepatitis C Virus (HCV) Kidney or Liver Transplant Recipients, Genotype 1, 2, 3, 4, 5, OR 6: Harvoni oral pellets were added to criteria for NS5A-Experienced, NS3/4-Naïve. For patients with genotype 3 HCV, Sovaldi was clarified to include tablets and oral pellets.	08/19/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hepatitis C – Ribavirin Prior Authorization Policy

- ribavirin tablets (generics)
- Moderiba™ (ribavirin tablets and dose packs – AbbVie, generics; obsolete 05/16/2018)
- ribavirin capsules (generics)
- Rebetol® (ribavirin oral solution – Schering Plough; obsolete 07/31/2019)
- Ribasphere® (ribavirin tablets and capsules – Kadmon, generics; obsolete 01/31/2020 [capsules], 01/01/2019 [tablets])

REVIEW DATE: 09/02/2020

OVERVIEW

Ribavirin is an antiviral agent with direct antiviral activity in tissue culture against many RNA viruses.[1-3] Ribavirin increases the mutation frequency in the genomes of several viruses and ribavirin triphosphate inhibits hepatitis C virus (HCV) polymerase in a biochemical reaction. The products contained in this Prior Authorization policy are indicated for use in combination with pegylated interferons or interferon for the treatment of chronic HCV in adults and children with compensated disease. Ribavirin remains a component of some regimens for the management of HCV.[5] The specific indications vary slightly among the oral ribavirin products:

- Rebetol oral solution and capsules are indicated in combination with PegIntron® (peginterferon alfa-2b injection) or Intron A® (interferon alfa-2b injection) for the treatment of chronic HCV in patients ≥ 3 years of age with compensated liver disease.[1]
- Ribavirin tablets in combination with Pegasys® (peginterferon alfa-2a) are indicated for the treatment of patients ≥ 5 years of age with chronic HCV with compensated liver disease who have not previously been treated with interferon alfa.[2]
- Ribasphere is indicated in adults in combination with Pegasys for the treatment of compensated chronic HCV in patients previously untreated with interferon alfa.[3]

Other Systemic Viral Infections

Ribavirin has been used off-label to treat other systemic viral infections including herpes simplex virus, respiratory syncytial virus[2,6,7], human metapneumovirus infection[8-9], adenovirus[8], influenza, severe acute respiratory syndrome, coronavirus, La Crosse encephalitis, Nipah encephalitis, Lassa fever[10,13], hemorrhagic fever with renal syndrome[10], Crimean-Congo hemorrhagic fever[10,11], Bolivian hemorrhagic fever[10], and hantavirus pulmonary infection[10,12] plus a variety of other systemic viral infections.[5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of ribavirin. The intent of this Prior Authorization program is to ensure ribavirin is not used in the absence of an alfa interferon or a direct-acting antiviral for the treatment of hepatitis C virus (HCV). All approvals are provided for 1 year unless otherwise noted below. Because of the specialized skills required for evaluation and diagnosis of patients being treated with ribavirin, as well as the monitoring required for adverse events and efficacy, approval requires ribavirin (for hepatitis C indications) to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: The use of a pegylated interferon or non-pegylated interferon or a direct-acting antiviral for hepatitis C virus (HCV) in the past 130 days. This is used as a surrogate marker for HCV. If the criteria for prior use of a pegylated interferon or non-pegylated interferon or direct-acting antiviral for HCV are not met at the point-of-service, coverage will be determined by Prior Authorization criteria.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of ribavirin is recommended in those who meet the following criteria:

FDA-Approved Indications

60. Hepatitis C Virus (HCV). Approve for 1 year if the patient meets the following criteria (A and B):

- **A)** Patient meets ONE of the following criteria (i or ii):
  - **i.** The medication is prescribed in combination with interferon alfa or peginterferon alfa; OR
    Note: Examples of interferon alfa or peginterferon alfa are Intron A (interferon alfa 2-b injection), Pegasys (pegylated interferon alfa-2a injection), PegIntron (pegylated interferon alfa-2b injection).
  - **ii.** Ribavirin is prescribed in combination with a direct-acting antiviral for hepatitis C virus (HCV); AND
    Note: Examples of direct-acting antivirals for HCV are Epclusa (velpatasvir/sofosbuvir tablets), Sovaldi (sofosbuvir tablets/oral pellets), Harvoni (ledipasvir/sofosbuvir tablets/oral pellets), Viekira Pak (paritaprevir/ombitasvir/ritonavir tablets + dasabuvir, co-packaged), Zepatier (elbasvir/grazoprevir tablets).
- **B)** Ribavirin is prescribed by or in consultation with a gastroenterologist, hepatologist, liver transplant physician, or infectious diseases physician.

Other Uses with Supportive Evidence

61. Other Systemic Viral Infections. Approve for 1 year.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of ribavirin is not recommended in the following situations:

77. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Rebetol® capsules and oral solution [prescribing information]. Whitehouse Station, NJ: Merk & Co., Inc.; January 2020.
2. Mori T, Nakamura Y, Kato, et al. Oral ribavirin therapy for lower respiratory tract infection of respiratory syncytial virus complicating bronchiolitis obliterans after allogeneic hematopoietic stem cell transplantation. *Int J Hematol*. 2011:93:132-134.
3. Ribasphere® [prescribing information]. Warendale, PA: Kadmon Pharmaceuticals; September 2017.
4. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. Testing, managing, and treating hepatitis C. Updated November 6, 2019. Available at: http://www.hcvguidelines.org. Accessed on August 19, 2020.

5. Razonable RR. Antiviral drugs for viruses other than human immunodeficiency virus. *Mayo Clin Proc.* 2011;86(10:1009-1026.
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7. Khanna N, Widmer AF, Decker M, et al. Respiratory syncytial virus infection in patients with hematological disease: Single-center study and review of the literature. *Clin Infect Dis.* 2008;46:402-412.
8. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant*. 2009;15:1143-1238.
9. Shahda S, Carlos WG, Kiel PJ, Khan BA, and Hage CA. The human metapneumovirus: a case series and review of the literature. *Transpl Infect Dis.* 2011;13(3):324-328.
10. Ippolit G, Feldmann H, Lanini S, et al. Viral hemorrhagic fevers: advancing the level of treatment. *BMC Med.* 2012;10:31.
11. Ergonul O, Keske S, Celdir MG, et al. Systematic review and meta-analysis of postexposure prophylaxis for Crimean-Congo Hemorrhagic Fever Virus among healthcare workers. *Emerg Infect Dis.* 2018;24(9):1642-1648.
12. The Centers for Disease Control and Prevention. Hantavirus. Available at: https://www.cdc.gov/hantavirus/hfrs/index.html. Accessed on September 16, 2019.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	Hepatitis C Virus (HCV): Removed Infergen from list of examples with which ribavirin can be prescribed (obsolete > 3 years).	09/26/2018
Annual revision	No criteria changes.	09/25/2019
Annual revision	**Hepatitis C Virus**. Updated the "note" section to list "examples are".	09/02/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hepatitis C – Sovaldi Prior Authorization Policy
- Sovaldi® (sofosbuvir tablets and oral pellets – Gilead)

REVIEW DATE: 01/13/2021

OVERVIEW

Sovaldi, a hepatitis C virus (HCV) nucleotide analog non-serine (NS)5B polymerase inhibitor, is indicated for the following uses:[1]

- Treatment of **genotype 1, 2, 3 or 4 chronic HCV infection as a component of a combination antiviral treatment**.
- Treatment of **pediatric patients ≥ 3 years of age with genotype 2 or 3 chronic HCV infection without cirrhosis or with compensated cirrhosis in combination with ribavirin**.

The place in therapy for Sovaldi has greatly lessened or is non-existent in some cases due to the availability of other direct-acting antivirals (DAAs) with greater efficacy for many genotypes. However, Sovaldi is the only DAA indicated in pediatric patients ≥ 3 years and < 6 years with genotype 2 or 3 chronic HCV (other DAAs are indicated in patients ≥ 6 years of age).

The recommended dose of Sovaldi tablets is one 400 mg tablet taken orally once daily with or without food.[1] The recommended dosage of Sovaldi tablets or oral pellets in pediatric patients ≥ 3 years of age with genotype 2 or 3 HCV is based on weight, and is to be taken orally once daily in combination with ribavirin. Sovaldi should be used in combination with weight-based ribavirin or peginterferon + ribavirin for the treatment of chronic HCV in adults. Regimens with Sovaldi + peginterferon + ribavirin or Sovaldi + weight-based ribavirin are no longer recommended in treatment guidelines with the exception of pediatric patients due to inferior efficacy compared with other all-oral regimens for all genotypes. Sovaldi + weight-

based ribavirin is indicated in pediatric patients with genotype 2 or 3 chronic HCV and has a unique role in such patients. Table 1 provides pediatric dosing.

Table 1. Sovaldi Treatment Regimen in Pediatric Patients (≥ 3 years of age).[1]

	Patient Population	Treatment and Duration
Genotype 2	Treatment-naïve and treatment experienced without cirrhosis or with compensated cirrhosis (Child-Pugh A)	Sovaldi + ribavirin x 12 weeks
Genotype 3	Treatment-naïve and treatment experienced without cirrhosis or with compensated cirrhosis (Child-Pugh A)	Sovaldi + ribavirin x 24 weeks

Guidelines

The American Association for the Study of Liver Diseases (AASLD) guidelines only recommend Sovaldi in the following instances:[2] Currently, Sovaldi + ribavirin remains the only FDA-approved DAA for children ≥ 3 to < 6 years of age with genotype 2 or 3 infection. However, FDA approval of Epclusa and Mavyret for children beginning at ≥ 3 years of age are anticipated in the future. The HCV guidance panel recommends delaying treatment pending approval of a pangenotypic regimen unless there is a compelling need for immediate antiviral treatment of children ≥ 3 to < 6 years of age with genotype 2 or 3 infection.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Sovaldi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Sovaldi as well as the monitoring required for adverse events and efficacy, approval requires Sovaldi to be prescribed by or in consultation with a physician who specialized in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sovaldi is recommended in those who meet the following criteria:

FDA-Approved Indications

47. Chronic Hepatitis C Virus (HCV) Genotype 2, Pediatric Patients. Approve for 12 weeks if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 3 years of age and < 18 years of age; AND
- **B)** Patient does not have decompensated cirrhosis (Child-Pugh B or C). [Coverage is provided for patients without cirrhosis or with compensated {Child-Pugh A} cirrhosis]; AND
- **C)** The medication will be prescribed in combination with ribavirin; AND
- **D)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

48. Chronic Hepatitis C Virus (HCV) Genotype 3, Pediatric Patients. Approve for 24 weeks if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 3 years of age and < 18 years of age; AND
- **B)** Patient does not have decompensated cirrhosis (Child-Pugh B or C). [Coverage is provided for patients without cirrhosis or for patients with compensated {Child-Pugh A} cirrhosis]; AND
- **C)** The medication will be prescribed in combination with ribavirin; AND
- **D)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

Other Uses with Supportive Evidence

3. **Patient Has Been Started on Sovaldi.** Approve for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications or Other Uses with Supportive Evidence). Approve the duration described above to complete a course therapy (e.g., a patient who should receive 12 weeks, and has received 3 weeks should be approved for 9 weeks to complete their 12-week course).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sovaldi is not recommended in the following situations:

1. **HCV (any genotype), Combination use with Direct-Acting Antivirals (DAAs) Other than or ribavirin.** In adults with genotype 3 chronic HCV with compensated cirrhosis who are peginterferon/ribavirin-experienced, Zepatier (elbasvir/grazoprevir tablets) + Sovaldi ± ribavirin is an alternative recommendation.[2] The C-ISLE study evaluated Zepatier + Sovaldi ± ribavirin, for 8 weeks to 16 weeks in treatment-naive or -experienced, genotype 3 patients with compensated cirrhosis (n = 100). The study included 53 patients with a history peginterferon/ribavirin failure. Treatment-experienced patients were randomized to 12 weeks of Zepatier + Sovaldi, 12 weeks of Zepatier + Sovaldi + weight-based ribavirin, or 16 weeks of Zepatier + Sovaldi. All three treatment arms had 100% SVR on the per protocol analysis, with 17 patients in each arm. Mavyret (glecaprevir/pibrentasvir tablets) and Vosevi (sofosbuvir/velpatasvir/voxilaprevir tablets) are recommended regimens in this setting; Mavyret is FDA-approved. In adults with any genotype chronic HCV with or without compensated cirrhosis who have failed treatment with Mavyret, retreatment with Mavyret + Sovaldi + ribavirin is a recommended regimen based on data from an ongoing Phase IIIb study evaluating the safety and efficacy of Mavyret + Sovaldi + weight-based ribavirin as a 12- or 16-week retreatment regimen for patients who experienced virologic failure to Mavyret within the context of a previous clinical trial. Non-cirrhotic Mavyret non-responders with genotype 1, 2, 4, 5, or 6 who were naive to protease and NS5A inhibitors received 12 weeks Mavyret + Sovaldi and weight-based ribavirin. Patients with genotype 3, and/or compensated cirrhosis, and/or protease/NS5A experience (prior to their initial glecaprevir/pibrentasvir treatment) received 16 weeks of therapy with the same regimen. In a preliminary analysis, 96% (n = 22/23) of these patients achieved SVR12 with a single relapse in a cirrhotic patient with genotype 1a. Vosevi is also a recommended regimen in this instance and it is FDA-approved.

2. **Life Expectancy < 12 Months Due to Non-Liver Related Comorbidities.** According to AASLD guidance, little evidence exists to support initiation of HCV treatment in patients with limited life expectancy (< 12 months) due to non-liver-related comorbid conditions.[2] For these patients, the benefits of HCV treatment are unlikely to be realized, and palliative care strategies should take precedence.

3. **Monotherapy with Sovaldi.** Sovaldi is indicated as a component of a combination antiviral treatment regimen for HCV.[1]

4. **Pediatric Patients (Age < 3 years).** The safety and efficacy of Sovaldi have not been established in pediatric patients < 3 years of age.[1]

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

34. Sovaldi® tablets and oral pellets [prescribing information]. Foster City, CA: Gilead; March 2020.
2. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. Testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org. Updated August 20, 2020. Accessed on: December 14, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	Genotype 1 chronic HCV: Criteria to approve Sovaldi with Olysio were removed. Genotype 1 recurrent HCV: Criteria to approve Sovaldi with Olysio were removed For conditions not recommended for approval, "HCV (any genotype), Combination use with Direct-Acting Antivirals (DAAs) Other than Daklinza, Olysio, or ribavirin", Olysio was removed from this list.	03/06/2019
Selected revision	Chronic Hepatitis C Virus (HCV) Genotype 2, Pediatric Patients: Age indication revised to include patients ≥ 3 years of age. Chronic Hepatitis C Virus (HCV) Genotype 3, Pediatric Patients: Age indication revised to include patients ≥ 3 years of age. In conditions not recommended for coverage: Pediatric Patients (Age < 12 years OR weighing < 35 kg): Age indication revised to < 3 years, weight requirement removed.	09/04/2019
Annual revision	No criteria changes	03/25/2020
Early annual revision	Chronic Hepatitis C Virus (HCV) Genotype 2, Pediatric Patients: an upper age limit of < 18 years of age was added. Chronic Hepatitis C Virus (HCV) Genotype 3, Pediatric Patients: an upper age limit of < 18 years of age was added. Chronic Hepatitis C Virus (HCV) Genotype 1, Adults: Criteria were removed. Chronic Hepatitis C Virus (HCV) Genotype 3, Adults: Criteria were removed. Recurrent Hepatitis C Virus (HCV) Post-Liver Transplantation, Genotype 1, 2, or 3: Criteria were removed. Hepatitis C Virus (HCV) [any genotype], Combination use with Direct-Acting Antivirals (DAAs) Other than Daklinza or ribavirin: Daklinza was removed from this condition not recommended for coverage.	01/13/2021

AASLD – American Association for the Study of Liver Diseases; HCV – Hepatitis C virus; WBR – Weight-based ribavirin; PA – Prior Authorization; HCC – Hepatocellular carcinoma.

PRIOR AUTHORIZATION POLICY

POLICY: Hepatitis C – Viekira Pak Prior Authorization Policy

- Viekira Pak™ (ombitasvir/paritaprevir/ritonavir tablets; dasabuvir tablets [co-packaged] – AbbVie)

REVIEW DATE: 09/02/2020

OVERVIEW

Viekira Pak is indicated for the treatment of patients with genotype 1 chronic hepatitis C virus (HCV).[1] Viekira Pak is indicated in patients with genotype 1b without cirrhosis or with compensated cirrhosis or with genotype 1a without cirrhosis or with compensated cirrhosis for use in combination with ribavirin. Viekira Pak contains ombitasvir, an HCV NS5A inhibitor, paritaprevir, an HCV NS3/4A protease inhibitor, ritonavir, a cytochrome P450 (CYP)3A inhibitor and dasabuvir, an HCV non-nucleoside NS5B palm polymerase inhibitor.

The recommended dose of Viekira Pak is two co-formulated ombitasvir/paritaprevir/ritonavir tablets once daily (in the morning) and one dasabuvir tablet twice daily (morning and evening). When administered with Viekira Pak, the recommended dose of ribavirin is weight-based. For patients with HCV/human immunodeficiency virus (HIV)-1 co-infection the recommendations are the same as for those without co-infection. Of note, product labeling notes that some patients with genotype 1a with cirrhosis may be treated

for 12 weeks with Viekira Pak + weight-based ribavirin based on data from the TURQUOISE-II trial. In liver transplant recipients with normal hepatic function and mild fibrosis (Metavir fibrosis score ≤ 2) the recommended duration of therapy with Viekira Pak is 24 weeks, irrespective of HCV genotype 1 subtype.

Table 1. FDA-Approved Regimens and Treatment Duration for Viekira Pak.[1,5]

Patient Population	Treatment*	Duration
Genotype 1a, without cirrhosis	Viekira Pak + WBR	12 weeks
Genotype 1a, with cirrhosis	Viekira Pak + WBR	24 weeks**
Genotype 1b, with or without cirrhosis	Viekira Pak	12 weeks

* Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection; WBR – Weight-based ribavirin; ** A 12 week treatment duration may be considered for some patients based on prior treatment history.

Guidelines

Viekira Pak is not addressed in the American Association for the Study of Liver Diseases (AASLD) Guidelines recommended (or alternative) regimens are detailed in the Hepatitis C Virus Direct-Acting Antivirals Therapy Class Summary.[2] Viekira Pak is only recognized in the guidelines as not recommended for use in patients with decompensated cirrhosis (Child-Pugh B or C).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Viekira Pak. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Viekira Pak as well as the monitoring required for adverse events and efficacy, approval requires Viekira Pak to be prescribed by or in consultation with a physician who specialized in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Viekira Pak is recommended in those who meet the following criteria:

FDA-Approved Indications

62. Chronic Hepatitis C Virus (HCV) Genotype 1a. Approve for the duration noted if the patient meets the following criteria (A, B, C and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The medication is prescribed in combination with ribavirin; AND
- **C)** Patient meets ONE of the following criteria (i or ii):
  - **i.** Patient does not have cirrhosis: Approve for 12 weeks; OR
  - **ii.** Patient has cirrhosis: Approve for 24 weeks; AND
- **D)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

63. Chronic Hepatitis C Virus (HCV) Genotype 1b. Approve for 12 weeks if the patient meets the following criteria (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

64. Recurrent Hepatitis C Virus (HCV) Post-Liver Transplantation, Genotype 1. Approve for 24 weeks if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Viekira Pak is prescribed in combination with ribavirin; AND
- **C)** Viekira Pak is prescribed by or in consultation with one of the following prescribers who is affiliated with a transplant center[2]: a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

65. Patient Has Been Started on Viekira Pak. Approve Viekira Pak for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications or Other Uses with Supportive Evidence). Approve the duration described above to complete a course of therapy (e.g., a patient who should receive 12 weeks, and has received 3 weeks should be approved for 9 weeks to complete their 12-week course).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Viekira Pak is not recommended in the following situations:

1. **Hepatitis C Virus (HCV), Child-Pugh Class B or Child-Pugh Class C Liver Disease (Moderate or Severe Hepatic Impairment).** Viekira Pak is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C).[1] The AASLD recommend *against* the use of Viekira Pak in patients with chronic hepatitis C virus (HCV) with decompensated cirrhosis (Child-Pugh Class B or C). On October 22, 2015 the FDA issued a safety communication about the risk of serious liver injury when Viekira Pak or Technivie® (paritaprevir/ritonavir/ombitasvir tablets) are used in patients with moderate or severe hepatic impairment.[3] Hepatic decompensation and liver failure in patients with underlying liver cirrhosis have been reported with the use of Viekira Pak and Technivie. Some of these events have resulted in liver transplant or death. These serious outcomes were reported mostly in patients taking Viekira Pak who had evidence of advanced cirrhosis even before starting treatment. Since the approvals of Viekira Pak in December 2014 and Technivie in July 2015, at least 26 worldwide cases submitted to the FDA Adverse Event Reporting System (FAERS) were considered to be possibly or probably related to Viekira Pak or Technivie. In most of the cases, liver injury occurred within 1 to 4 weeks of starting treatment. Some of the cases occurred in patients for whom these medicines were contraindicated or not recommended. Among these 26 cases 5 were reported in the US.[4]

2. **Hepatitis C Virus (HCV) [Any Genotype], Combination with Any Other Direct-Acting Antivirals (DAAs) Not Including Ribavirin.** Viekira Pak provide a complete antiviral regimen for patients with genotype 1 HCV. Viekira Pak is indicated with ribavirin for some patients. In the opinion of a specialist physician reviewing the data we have adopted this criterion.

3. **Life Expectancy Less Than 12 Months Due to Non-Liver Related Comorbidities.** Patients with limited life expectancy for whom HCV therapy would not improve symptoms or prognosis do not require treatment.[2] According to AASLD guidance, the panel continues to recommend treatment for all patients with chronic HCV infection, *except* those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. For these patients, the benefits of HCV treatment are unlikely to be realized, and palliative care strategies should take precedence.

5. **Pediatric Patients (Age < 18 Years).** The safety and efficacy of Viekira Pak have not been established in pediatric patients < 18 years of age.[1]

6. **Retreatment with Viekira Pak in Patients Who Have Previously Received Viekira Pak, Viekira XR, or Technivie** (e.g., retreatment in prior null responders, prior partial responders, prior relapse patients, patients who have not completed a course of therapy due to an adverse reaction or for other reasons). Technivie, Viekira Pak, and Viekira XR contain the same active ingredients; Viekira Pak and Viekira XR additionally contain dasabuvir.

7. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

35. Viekira Pak™ tablets [prescribing information]. North Chicago, IL: AbbVie, Inc.; December 2019.
2. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. Testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org. Updated November 6, 2019. Accessed on August 24, 2020.
3. Food and Drug Administration (FDA). FDA Drug Safety Communication: FDA warns of serious liver injury risk with hepatitis C treatments Viekira Pak and Technivie. October 22, 2015. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm468634.htm. Accessed on August 24, 2020.
4. Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med.* 2014;370:1604-1614.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	No criteria changes.	10/10/2018
Annual revision	Viekira XR was removed from the policy. Title of the policy re-named to Viekira Pak.	10/02/2019
Annual revision	Conditions Not Recommended for Approval. Retreatment with Viekira Pak or Viekira XR in Patients Who Have Previously Received Viekira Pak, Viekira XR, or Technivie (e.g., retreatment in prior null responders, prior partial responders, prior relapse patients, patients who have not completed a course of therapy due to an adverse reaction or for other reasons). Retreatment with Viekira XR was removed from this statement.	09/02/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hepatitis C – Vosevi Prior Authorization Policy

- Vosevi® (sofosbuvir/velpatasvir/voxilaprevir tablets – Gilead)

REVIEW DATE: 08/19/2020

OVERVIEW

Vosevi is a direct-acting-antiviral (DAA) indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor and for patients with genotype 1a or 3 infection and who have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor. Additional benefit of Vosevi over Epclusa® (sofosbuvir/velpatasvir tablets) was not shown in adults with genotype 1b, 2, 4, 5, or 6 infection previously treated with sofosbuvir without an NS5A inhibitor. The recommended dosage of Vosevi is one tablet, taken orally, once daily (QD) with food for 12 weeks.

Vosevi contains sofosbuvir, a nucleotide analog NS5B polymerase inhibitor, velpatasvir, an HCV NS5A inhibitor, and voxilaprevir, a new HCV NS3/4A protease inhibitor. Sofosbuvir has previously been available as Sovaldi® (sofosbuvir tablets) and as part of Harvoni® (sofosbuvir/ledipasvir tablets) and Epclusa. Velpatasvir has previously been available as part of Epclusa.

Guidelines

For the most up-to-date guideline information always refer to the American Association for the Study of Liver Diseases (AASLD) guidelines.[3] Vosevi is recommended in the circumstances outlined below (Table 1).

Table 1. AASLD Recommended and Alternative Regimens that Include Vosevi.[3]

DAA	Duration	FDA Approved (Y/N)	AASLD Level of Evidence
Genotype 1 Chronic HCV Previously Treated with Non-NS5A Sovaldi, Adults – Recommended			
Vosevi	12 weeks (GT1a ± compensated cirrhosis)	Y	Class I, Level A

Genotype 1 Chronic HCV Previously Treated with NS5A, Adults – Recommended			
Vosevi	12 weeks (± compensated cirrhosis)	Y	Class I, Level A
Genotype 2 Chronic HCV Previously Treated with Sovaldi + NS5A, Adults – Recommended			
Vosevi	12 weeks (± compensated cirrhosis)	N	Class I, Level B
Genotype 3 Chronic HCV Treatment-Naïve Adults – Alternative			
Vosevi	12 weeks (compensated cirrhosis, if Y93H is present)	N	Class IIa, Level B
Genotype 3 Chronic HCV Previously Treated with Pegylated Interferon/Ribavirin, Adults – Recommended			
Vosevi	12 weeks (compensated cirrhosis)	N	Class IIb, Level B
Genotype 3 Chronic HCV Previously Treated with Pegylated Interferon/Ribavirin, Adults – Alternative			
Vosevi	12 weeks (no cirrhosis)	N	Class IIb, Level B
Genotype 3 Chronic HCV Previously Treated with Sovaldi + WBR, Adults – Recommended			
Vosevi	12 weeks (± compensated cirrhosis)	Y	Class I, Level B
Genotype 3 Chronic HCV DAA-Experienced, Including NS5A, Adults – Recommended			
Vosevi	12 weeks (± compensated cirrhosis)	Y	Class I, Level A
Vosevi + WBR	12 weeks (prior NS5A failures with cirrhosis)	N	Class IIa, Level C
Genotype 4 Chronic HCV DAA-Experienced, Including NS5A, Adults – Recommended			
Vosevi	12 weeks (± compensated cirrhosis)	Y	Class I, Level A

Table 1 (continued). AASLD Recommended and Alternative Regimens that Include Vosevi.[3]

DAA	Duration	FDA Approved (Y/N)	AASLD Level of Evidence
Genotype 5/6 Chronic HCV DAA-Experienced, Including NS5A, Adults – Recommended			
Vosevi	12 weeks (± compensated cirrhosis)	N	Class IIA, Level B
Genotype 1, 2, 3, 4, 5, 6 Recurrent HCV Post-Liver Transplant, DAA-Experienced ± Compensated Cirrhosis, Adults – Recommended			
Vosevi	12 weeks	N	Class I, Level C
Genotype 1, 2, 3, 4, 5, 6 HCV Kidney Transplant Recipients, DAA-Experienced, Adults – Recommended			
Vosevi	12 weeks (± compensated cirrhosis)	N	Class IIa, Level C

AASLD – American Association for the Study of Liver Diseases; FDA – Food and Drug Administration; Y – Yes; N – No; HCV – Hepatitis C virus; DAA – Direct-acting antiviral; WBR – Weight-based ribavirin.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vosevi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vosevi as well as the monitoring required for adverse events and efficacy, approval requires Vosevi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vosevi is recommended in those who meet the following criteria:

FDA-Approved Indications

66. Chronic Hepatitis C Virus (HCV) Genotype 1b, 2, 4, 5, or 6. Approve for 12 weeks if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient does not have cirrhosis OR the patient has compensated cirrhosis (Child-Pugh A);
- **C)** Patient had a prior null response, prior partial response, or had relapse after prior treatment with an HCV direct-acting antiviral regimen containing an NS5A inhibitor; AND
  Note: Examples of direct-acting antivirals that are, or contain, an NS5A inhibitor include: Daklinza (daclatasvir tablets), Epclusa (sofosbuvir/velpatasvir tablets), Harvoni (ledipasvir/sofosbuvir tablets/oral pellets), Mavyret (glecaprevir/pibrentasvir tablets), Viekira Pak (ombitasvir/paritaprevir/ritonavir tablets; dasabuvir tablets, co-packaged), Zepatier (elbasvir/grazoprevir tablets).
- **D)** Vosevi is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

67. Chronic Hepatitis C Virus, Genotype 1a or 3. Approve for 12 weeks if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient does not have cirrhosis OR the patient has compensated cirrhosis (Child-Pugh A); AND
- **C)** Patient meets ONE of the following conditions (i or ii):
  - **i.** Patient had a prior null response, prior partial response, or had relapse after prior treatment with an HCV direct-acting antiviral regimen containing an NS5A inhibitor; OR
    Note: Examples of direct-acting antivirals that are, or contain, an NS5A inhibitor include: Daklinza (daclatasvir tablets), Epclusa (sofosbuvir/velpatasvir tablets), Harvoni (ledipasvir/sofosbuvir tablets/oral pellets), Mavyret (glecaprevir/pibrentasvir tablets), Viekira Pak (ombitasvir/paritaprevir/ritonavir tablets; dasabuvir tablets, co-packaged), Zepatier (elbasvir/grazoprevir tablets).

ii. Patient had a prior null response, prior partial response, or had relapse after prior treatment with an HCV DAA regimen containing Sovaldi (sofosbuvir tablets/oral pellets) + a non-NS5A inhibitor; AND
Note: Examples of regimens that contain Sovaldi (sofosbuvir tablets/oral pellets) + a non-NS5A inhibitor include: Sovaldi + NS3 inhibitors (Olysio [simeprevir capsules], Victrelis [boceprevir capsules], or Incivek [telaprevir tablets]) or Sovaldi + ribavirin ± pegylated interferon;

D) Vosevi is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

Other Uses with Supportive Evidence

68. Chronic Hepatitis C Virus (HCV) Genotype 1b, 2, 4, 5, or 6. Approve for 12 weeks in patients who meet the following criteria (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient does not have cirrhosis OR the patient has compensated cirrhosis (Child-Pugh A); AND

C) Patient had a prior null response, prior partial response, or had relapse after prior treatment with an HCV DAA regimen containing Sovaldi (sofosbuvir tablets/oral pellets) + a non-NS5A inhibitor; AND
Note: Examples of regimens that contain Sovaldi (sofosbuvir tablets/oral pellets) + a non-NS5A inhibitor include: Sovaldi + NS3 inhibitors (Olysio [simeprevir capsules], Victrelis [boceprevir capsules], or Incivek [telaprevir tablets]) or Sovaldi + ribavirin ± pegylated interferon;

D) Vosevi is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician.

4. Patient Has Been Started on Vosevi. Approve for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications or Other Uses with Supportive Evidence). Approve the duration described above to complete a course therapy (e.g., a patient who should receive 12 weeks, and has received 3 weeks should be approved for 9 weeks to complete their 12-week course).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vosevi is not recommended in the following situations:

1. Hepatitis C Virus (HCV) [any genotype], Combination with Any Other Direct-Acting Antivirals (DAAs). Vosevi provides a complete antiviral regimen.

38. Life Expectancy Less Than 12 Months Due to Non-Liver Related Comorbidities. According to the AASLD guidelines, patients with a limited life expectancy that cannot be remediated by HCV treatment, liver transplantation, or another directed therapy do not require antiviral treatment.[3] Patients with a short life expectancy owing to liver disease should be managed in consultation with an expert. Chronic HCV is associated with a wide range of comorbid conditions. Little evidence exists to support initiation of HCV treatment in patients with a limited life expectancy (< 12 months) owing to non-liver-related comorbid conditions. For these patients, the benefits of HCV treatment are unlikely to be realized and palliative care strategies should take precedence.

3. Pediatric Patients (Age < 18 Years). The safety and efficacy of Vosevi have not been established in pediatric patients < 18 years of age.[1]

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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3. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. Testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org. Updated November 6, 2019. Accessed on August 11, 2020.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes	08/01/2018
Update	Addition of generics to Epclusa and Harvoni	12/14/2018
Annual revision	Chronic Hepatitis C Virus, Genotype 1b, 2, 4, 5, or 6: Mavyret was added to the Note of products that contain an NS5A inhibitor. Chronic Hepatitis C Virus, Genotype 1a or 3: Mavyret was added to the Note of products that contain an NS5A inhibitor.	08/28/2019
Annual revision	Chronic Hepatitis C Virus (HCV) Genotype 1b, 2, 4, 5, or 6: Note addressing NS5A-containing regimens was updated from an inclusive list to a list of examples. Technivie and Viekira XR were removed from the note. References to Harvoni and Epclusa "brand or generic" was removed. Harvoni oral pellets were added to the note. Chronic Hepatitis C Virus, Genotype 1a or 3: Note addressing NS5A-containing regimens was updated from an inclusive list to a list of examples. Technivie and Viekira XR were removed from the note. References to Harvoni and Epclusa "brand or generic" was removed. Harvoni oral pellets were added to the note. Note addressing Sovaldi and a non-NS5A inhibitor containing regimens was updated from an inclusive list to a list of examples. Chronic Hepatitis C Virus (HCV) Genotype 1b, 2, 4, 5, or 6. Note addressing Sovaldi and a non-NS5A inhibitor containing regimens was updated from an inclusive list to a list of examples.	08/19/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hepatitis C – Zepatier® (grazoprevir/elbasvir tablets – Merck)

TAC APPROVAL DATE: 03/25/2020

OVERVIEW

Zepatier is an oral fixed-dose combination tablet containing grazoprevir, a second generation protease inhibitor and elbasvir, an NS5A inhibitor, indicated with or without ribavirin for the treatment of genotypes 1 and 4 chronic hepatitis C virus (HCV) in adults.[1] Zepatier is contraindicated in patients with Child-Pugh B or C liver disease (decompensated cirrhosis). Zepatier is also contraindicated with inhibitors of organic anion transporting polypeptides 1B1/3 (OATP1B1/3) that are known or expected to significantly increase grazoprevir plasma concentrations, strong inducers of cytochrome P450 (CYP)3A, and efavirenz.

Dosing

The recommended dosage of Zepatier is one co-formulated tablet containing 50 mg of grazoprevir and 100 mg of elbasvir once daily (QD) with or without food.[1] The duration of treatment is outlined below (Table 1) and is dependent on the patient population. Prior to initiating Zepatier in patients with genotype 1a infection, testing for the NS5A resistance associated polymorphism is recommended to guide treatment duration. In patients with genotype 1a and this polymorphism present at baseline, 12 weeks of treatment with Zepatier resulted in lower rates of sustained viral response 12 weeks after treatment completion (SVR12) relative to patients with genotype 1a without the presence of this baseline polymorphism.

Table 1. Recommended Zepatier Dosage Regimens for the Treatment of Genotype 1 or 4 Chronic HCV.[1]

Genotype	Treatment History	Baseline NS5A Polymorphism	Treatment Regimen	Treatment Duration
1a	TN/PR-experienced* without NS5A polymorphisms†	No†	Zepatier	12 weeks
1a	TN/PR-experienced* with baseline NS5A polymorphisms†	Yes†	Zepatier + ribavirin‡	16 weeks
1a§ or 1b	PR + HCV PI-experienced$^{\beta}$	NA	Zepatier + ribavirin‡	12 weeks
1b	TN/TE*	NA	Zepatier	12 weeks
4	TN	NA	Zepatier	12 weeks
4	PR-experienced*	NA	Zepatier + ribavirin‡	16 weeks

HCV – Hepatitis C virus; TN – Treatment naïve; PR- Pegylated interferon/ribavirin; * Patients who have failed treatment with PR; † NS5A resistance-associated polymorphisms at amino acid positions 28, 30, 31, or 93; ‡ For patients with creatinine clearance (CrCl) > 50 mL/min, the recommended dose of ribavirin is weight-based. For patients with CrCl ≤ 50 mL/min, including patients receiving hemodialysis, refer to the ribavirin prescribing information for the correct ribavirin dosage; § The optimal Zepatier-based treatment regimen and duration of therapy for PR + HCV protease inhibitor (PI)-experienced genotype 1a-infected patients with one or more baseline NS5A resistance-associated polymorphisms at positions 28, 30, 31, and 93 has not been established; PI – PI – Protease inhibitor; $^{\beta}$ Patients who have failed treatment with PR + and NS3/4A PI (i.e., Victrelis® [boceprevir capsules], Incivek® [telaprevir tablets], or Olysio® [simeprevir capsules]); NA – Not applicable.

Guidelines

The American Association for the Study of Liver Diseases (AASLD) recommended regimens are detailed in the *Hepatitis C Virus Direct-Acting Antivirals Therapy Class Summary*.[5] For the most up-to-date recommendations always consult the guidelines. NS5A RAS testing is recommended for genotype 1a-infected, treatment-naive or -experienced patients being considered for Zepatier. If present, a different regimen should be considered. Zepatier is recognized as a recommended treatment option in patients with genotype 1 or 4 chronic HCV in guidelines.[5]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Zepatier. Criteria are based on the guidance issued by American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA), prescribing information, clinical data, and expert review. Approval durations differ by baseline characteristics. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zepatier as well as the monitoring required for adverse events (AEs) and efficacy, approval requires Zepatier to be prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or liver transplant physician.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zepatier is recommended in those who meet the following criteria:

FDA-Approved Indications

39. Chronic Hepatitis C Virus (HCV) Genotype 1a. Approve for the specified duration below if patients meet the following criteria (A, B, and C):

- **i.** The patient is ≥ 18 years of age; AND
- **ii.** Zepatier is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician; AND
- **iii.** The patient meets ONE of the following criteria (i or ii):
  - **a)** Approve for 12 weeks if the patient meets ONE of the following conditions (a or b):

(1) Condition 1 (patients must meet [1] or [2], PLUS [3]):
   a. The patient is treatment-naïve; OR
   b. The patient has previously been treated with pegylated interferon + ribavirin *only*; AND
   c. The patient does NOT have a baseline NS5A polymorphism at ONE (or more) of the following the amino acid positions: 28, 30, 31, or 93; OR

(2) Condition 2 (patients must meet [1] and [2]):
   a. The patient has previously been treated with pegylated interferon + ribavirin and an HCV protease inhibitor; AND
   b. Zepatier will be prescribed in combination with ribavirin.

b) Approve for 16 weeks if the patient meets the following criteria (a or b, PLUS c and d):
(1) The patient is treatment-naïve; OR
(2) The patient has previously been treated with pegylated interferon + ribavirin *only*; AND
(3) The patient has a baseline NS5A polymorphism at ONE (or more) of the following amino acid positions: 28, 30, 31, or 93; AND
(4) Zepatier will be prescribed in combination with ribavirin.

40. Chronic Hepatitis C Virus (HCV) Genotype 1b. Approve for 12 weeks if patients meet the following criteria (A, B, and C):
i. The patient is ≥ 18 years of age; AND
ii. Zepatier is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician; AND
iii. The patient meets ONE of the following conditions (i or ii):
a) Condition 1 (patients must meet a or b):
(1) The patient is treatment-naïve; OR
(2) The patient has previously been treated with pegylated interferon + ribavirin *only*; OR
b) Condition 2 (patients must meet a and b):
(1) The patient has previously been treated with pegylated interferon + ribavirin + an HCV protease inhibitor; AND
(2) Zepatier will be prescribed in combination with ribavirin.

3. Chronic Hepatitis C Virus (HCV) Genotype 4. Approve for the duration specified below if patients meet the following criteria (A, B, and C):
A) The patient is ≥ 18 years of age; AND
B) Zepatier is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician;
C) The patient meets ONE of the following conditions (i or ii):
i. Approve for 12 weeks if the patient is treatment-naïve; OR
ii. Approve for 16 weeks if the patient has previously been treated with pegylated interferon and ribavirin for HCV and Zepatier will be prescribed in combination with ribavirin.

Other Uses with Supportive Evidence

4. **Patient Has Been Started on Zepatier.** Approve for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications or Other Uses with Supportive Evidence). Approve the duration described above to complete a course therapy (e.g., a patient who should receive 12 weeks, and has received 3 weeks should be approved for 9 weeks to complete their 12-week course).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Zepatier has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Hepatitis C Virus (HCV), Child-Pugh Class B or Child-Pugh Class C Liver Disease (Moderate or Severe Hepatic Impairment).** Zepatier is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C).[1]

2. **Hepatitis C Virus (HCV) [any genotype], Combination with Any Other Direct-Acting Antivirals (DAAs) [Not Including Ribavirin].** Zepatier provides a complete antiviral regimen for patients with genotype 1 and 4 chronic HCV.

4. **Life Expectancy Less Than 12 Months Due to Non-Liver Related Comorbidities.** According to AASLD guidance, little evidence exists to support initiation of HCV treatment in patients with limited life expectancy (less than 12 months) due to non–liver-related comorbid conditions.[5] For these patients, the benefits of HCV treatment are unlikely to be realized, and palliative care strategies should take precedence.

4. **Pediatric Patients (Age < 18 Years).** The safety and efficacy of Zepatier have not been established in pediatric patients < 18 years of age.[1] Guidelines recommend Harvoni (ledipasvir/sofosbuvir tablets) in pediatric patients with genotypes 1 or 4 chronic HCV.[5]

5. **Retreatment with Zepatier in Patients Who Have Previously Received Zepatier** (e.g., retreatment in prior null responders, prior partial responders, prior relapse patients, patients who have not completed a course of therapy due to an adverse reaction or for other reasons).

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Annual revision	No criteria changes	02/15/2017
Annual revision	No criteria changes	02/28/2018
Annual revision	No criteria changes	03/06/2019
Annual revision	No criteria changes	03/25/2020

TAC – Therapeutic Assessment Committee; * For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx.

PRIOR AUTHORIZATION POLICY

POLICY: Hepatology – Givlaari Prior Authorization Policy

- Givlaari™ (givosiran injection solution, for subcutaneous use – Alnylam Pharmaceuticals)

REVIEW DATE: 12/16/2020

OVERVIEW

Givlaari, an aminolevulinate synthase 1-directed small interfering RNA, is indicated for the treatment of patients ≥ 18 years of age with **acute hepatic porphyria** (AHP).[1]

Givlaari is a double-stranded small interfering RNA that causes degradation of aminolevulinate synthase 1 (ALAS1) mRNA in hepatocytes through RNA interference, reducing the elevated levels of liver ALAS1 mRNA.[1] This leads to reduced circulating levels of neurotoxic intermediates aminolevulinic acid and porphobilinogen, factors associated with attacks and other disease manifestations of AHP. In the pivotal trial, inclusion criteria specified a minimum of 2 porphyria attacks requiring hospitalization, urgent healthcare visit, or intravenous hemin administration at home in the 6 months prior to study entry. Hemin use during the study was permitted for the treatment of acute porphyria attacks.

Disease Overview

Porphyria is a group of metabolic disorders caused by abnormalities in the chemical steps that lead to the production of heme.[2] Heme is necessary for the transport of oxygen to cells in the body. If synthesis of heme is hindered, an accumulation of porphyrins or porphyrin precursors (intermediate chemicals) accumulates in the cells, resulting in oxygen depletion. AHPs are a subgroup of porphyrias in which the enzyme deficiency occurs within the liver.[3] AHPs include acute intermittent porphyria (AIP), variegate porphyria (VP), 5-aminolevulinic acid dehydratase deficiency porphyria (ALAD), and hereditary coproporphyria (HCP) and are characterized by acute neurovisceral symptoms with or without cutaneous manifestations.[3,4] Symptoms and treatments for AIP, VP, ALAD, and HCP are similar, however, VP and HCP patients often develop photosensitivity. Signs and symptoms of AHP usually occur intermittently and include abdominal pain, constipation, muscle weakness, pain in the arms and legs, insomnia, emotional complications, rapid pulse, and high blood pressure. Hospitalization is often required for acute attacks. Although most symptomatic patients with AHP have complete resolution of their symptoms between attacks, those with numerous recurrent occurrences may develop chronic pain. Due to the high prevalence of chronic kidney disease, serum creatinine and estimated glomerular filtration rate should be monitored annually for all symptomatic patients.

Guidelines

The Porphyrias Consortium of the National Institutes of Health's Rare Diseases Clinical Research Network has developed recommendations for evaluation and long-term management of AHPs (2017).[5] Initial assessments should include diagnostic confirmation by biochemical testing, subsequent genetic testing to determine the specific AHP, and a complete medical history and physical examination. Preventative measures should be taken to prevent attacks. Hemin therapy (e.g., Panhematin® [hemin injection for intravenous infusion]) is recommended for preventative management in AHP and treatment during acute attacks. Patients with ≥ four attacks per year are candidates for either prophylactic or "on demand" infusions. The need for ongoing prophylaxis should be assessed every 6 to 12 months. Repeated long term treatment with hemin therapy can lead to iron overload and contribute to hepatic damage and fibrosis. Carbohydrate loading (glucose tablets or dextrose solutions) has been used in early stages of an acute attack, but there are no clear data showing a benefit. Women with AHP can develop cyclic attacks correlated to the menstrual

cycle. Options to prevent these attacks include recognizing and removing exacerbating factors, a gonadotropin releasing-hormone analog, switching to a low dose hormonal contraceptive, or prophylactic hemin therapy infusions.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Givlaari. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Givlaari as well as the monitoring required for adverse events and long-term efficacy, approval requires Givlaari to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Givlaari is recommended in those who meet the following criteria:

FDA-Approved Indications

69. Acute Hepatic Porphyria. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):

- **A)** Patient is ≥ 18 years of age; AND
- **B)** Diagnosis of acute hepatic porphyria was confirmed by both of the following (i and ii):
  - **i.** Patient demonstrated clinical features associated with acute hepatic porphyria; AND
    Note: Examples of clinical features associated with acute intermittent porphyria include neurovisceral symptoms, blistering lesions, hepatic involvement, peripheral neuropathy, abdominal pain, constipation, muscle weakness, pain in the arms and legs.
  - **ii.** Patient meets one of the following (a or b):
    - **a)** Elevated urinary aminolevulinic acid (ALA) greater than the upper limit of normal; OR
    - **b)** Elevated urinary porphobilinogen (PBG) greater than the upper limit of normal; AND
- **C)** Prior to starting treatment with Givlaari, the patient has a history of one porphyria attack in the last 6 months that required a hospitalization, urgent healthcare visit, or intravenous hemin administration at home; AND
- **D)** Givlaari is prescribed by, or in consultation with a gastroenterologist, hepatologist, or a physician who specializes in acute hepatic porphyria.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Givlaari is not recommended in the following situations:

78. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

223. Givlaari™ injection solution [prescribing information]. Cambridge, MA: Alnylam Pharmaceuticals; November 2019.
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HISTORY

Type of Revision	Summary of Changes	Review Date

New Policy	--	12/18/2019
Selected Revision	**Acute Hepatic Porphyria:** The requirement for a history of one porphyria attack in the last 6 months that required hospitalization, urgent healthcare visit, or intravenous hemin administration at home was added to the criteria.	05/20/2020
Annual Revision	**Acute Hepatic Porphyria:** Criteria requiring diagnosis of acute hepatic porphyria was added to the policy.	12/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hepatology – Ocalvia Prior Authorization Policy

- Ocaliva® (obeticholic acid tablets – Intercept Pharmaceuticals)

REVIEW DATE: 07/22/2020

OVERVIEW

Ocaliva is indicated for the treatment of primary biliary cholangitis in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.[1] Ocaliva was approved for this indication under accelerated approval based on reduction in alkaline phosphatase. An improvement in survival or primary biliary cholangitis-related symptoms has not been established. The prescribing information notes that continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Disease Overview

Primary biliary cholangitis is a chronic, progressive, cholestatic liver disease in which autoimmune destruction of small and medium intrahepatic bile ducts leads to cholestasis.[3,4] Cholestasis eventually progresses to advanced fibrosis, cirrhosis, and liver failure.[3-5] The serologic hallmark of primary biliary cholangitis is the finding of anti-mitochondrial antibodies in the serum.[3,4] In the 5% to 10% of patients in which anti-mitochondrial antibodies is absent or present only in low titer, nearly all will have primary biliary cholangitis-specific antinuclear antibodies, including sp100 and gp210, which are present in over 30% of patients who are negative for anti-mitochondrial antibodies by indirect immunofluorescence. The biochemical hallmark of primary biliary cholangitis is the finding of an elevated alkaline phosphatase level.[5]

Clinical Efficacy

The pivotal study evaluated Ocaliva in adult patients with primary biliary cholangitis who either had an inadequate response to UDCA (93% of patients) or were unable to tolerate UDCA (7% of patients).[2] The primary efficacy endpoint (composite of alkaline phosphatase level < 1.67 times the upper limit of normal, ≥ 15% reduction in alkaline phosphatase, and a total bilirubin ≤ upper limit of normal at Month 12) was met by 46% and 47% of patients treated with Ocaliva 5 mg and Ocaliva 10 mg, respectively. There were significant reductions in alkaline phosphatase with both Ocaliva groups early in treatment and sustained throughout the 12-month study. Through Year 3, Ocaliva therapy has resulted in a sustained reduction in alkaline phosphatase.[2,6]

Guidelines

The American Association for the Study of Liver Disease guidelines for primary biliary cholangitis (2018) state that the diagnosis can be confirmed when patients meet two of the following criteria: 1) there is cholestasis as evidenced by alkaline phosphatase elevation; 2) anti-mitochondrial antibodies are present, or if negative for anti-mitochondrial antibodies, other primary biliary cholangitis-specific autoantibodies, including sp100 or gp210, are present; 3) there is histologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts. It is specifically noted that diagnosis in a patient who is negative for anti-mitochondrial antibodies does not require a liver biopsy if other diagnostic criteria are

met. Treatment with UDCA (available in the US as ursodiol) at a dose of 13 to 15 mg/kg/day orally is the recommended treatment for patients with primary biliary cholangitis who have abnormal liver enzyme values regardless of histologic stage.[3] Following 12 months of UDCA therapy, the patient should be evaluated to determine if second-line therapy is appropriate. It is estimated that up to 40% of patients have an inadequate response to UDCA; Ocaliva should be considered for these pateints. The European Association for the Study of the Liver guidelines for diagnosis and management of patients with primary biliary cholangitis (2017) make similar recommendations.[7]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Ocaliva. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ocaliva as well as the monitoring required for adverse events and long-term efficacy, approval requires Ocaliva to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ocaliva is recommended in those who meet the following criteria:

FDA-Approved Indications

49. Primary Biliary Cholangitis (also known as Primary Biliary Cirrhosis). Approve Ocaliva for the duration noted if the patient meets one of the following conditions (A or B):

41. Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. According to the prescriber, the patient has a diagnosis of primary biliary cholangitis as defined by TWO of the following (a, b, c):

a) Alkaline phosphatase is elevated above the upper limit of normal as defined by normal laboratory reference values;

b) Positive anti-mitochondrial antibodies or other primary biliary cholangitis-specific auto-antibodies, including sp100 or gp210, if anti-mitochondrial antibodies are negative;

c) Histologic evidence of primary biliary cholangitis from a liver biopsy; AND

iii. Patient meets ONE of the following criteria (a or b):

a) Patient has been receiving ursodiol therapy for ≥ 1 year and has had an inadequate response according to the prescriber; OR

b) According to the prescriber the patient is unable to tolerate ursodiol therapy; AND
Note: Examples of ursodiol therapy include ursodiol generic tablets and capsules, Urso 250®, Urso Forte® and Actigall®.

iv. The agent is prescribed by or in consultation with a gastroenterologist, hepatologist, or liver transplant physician.

42. Patient is Currently Receiving Therapy. Approve for 1 year if the patient has responded to Ocaliva therapy as determined by the prescriber.
Note: Examples of a response to Ocaliva therapy are improved biochemical markers of primary biliary cholangitis (e.g., alkaline phosphatase, bilirubin, gamma-glutamyl transpeptidase [GGT], aspartate aminotransferase [AST], alanine aminotransferase [ALT]).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ocaliva is not recommended in the following situations:

11. **Alcoholic Liver Disease**. There are no data available to support the use of Ocaliva in patients with alcoholic hepatitis. Ocaliva is not FDA-approved for this indication and current alcoholic liver disease guidelines from AASLD (2010) do not make recommendations regarding therapy with Ocaliva.[1,8] Additional well-controlled studies are needed.

12. **Nonalcoholic Fatty Liver Disease (NAFLD), including Nonalcoholic Fatty Liver (NAFL) or Nonalcoholic Steatohepatitis (NASH).** Ocaliva is not FDA-approved for this indication and current NAFLD guidelines from AASLD (2018) recommend against the off-label use of obeticholic acid to treat NASH until additional safety and efficacy data become available.[1,9]

13. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	No changes.	07/11/2018
Annual revision	• Primary Biliary Cholangitis: Wording in reference to "according to the prescribing physician" was changed to "according to the prescriber". For initial therapy approval, to confirm the diagnosis of primary biliary cholangitis, added that patients could be positive for anti-mitochondrial antibodies (AMAs) or other PBC-specific auto-antibodies including sp100 or gp210, if AMA is negative. Changed the approval duration for "Patients Currently Receiving Therapy" from 3 years to 1 year. Removed age requirement and specialist requirement from the criteria for "Patients Currently Receiving Therapy".	07/24/2019
Annual revision	No criteria changes.	07/22/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hereditary Angioedema – C1 Esterase Inhibitors (Intravenous) Prior Authorization Policy

- Berinert® (C1 esterase inhibitor [human] for IV use – CSL Behring)
- Cinryze® (C1 esterase inhibitor [human] for intravenous [IV] use – Shire/Takeda)

- Ruconest® (recombinant C1 esterase inhibitor for IV use – Pharming Healthcare, Inc.)

REVIEW DATE: 08/26/2020

OVERVIEW

Berinert, Cinryze, and Ruconest are C1 esterase inhibitor (C1-INH) replacement therapies for hereditary angioedema (HAE).[1-3] Cinryze and Berinert are human plasma-derived C1-INH; Ruconest is a recombinant C1-INH purified from milk of transgenic rabbits. Berinert is indicated for the treatment of acute abdominal, laryngeal, or facial attacks of HAE in adult and pediatric patients.[2] Cinryze is indicated for routine prophylaxis against angioedema attacks in pediatric, adolescent, and adult patients with HAE.[1] Ruconest is indicated for the treatment of acute HAE attacks in adult and adolescent patients.[3]

Of note, although Cinryze is labeled for use in the prophylactic setting and Berinert is labeled for use in the acute treatment setting, guidelines do not differentiate between these products. Plasma-derived C1-INH therapy is supported for both acute treatment and prophylactic therapy.[4,5,8,9] Additionally, use of Cinryze for acute treatment of acute HAE attacks has been reported in literature.[10]

Disease Overview

HAE due to C1-INH deficiency has two subtypes: HAE type I and HAE type II. HAE diagnosis can be confirmed by measuring functional C1-INH protein levels (usually < 50% of normal in patients with HAE), C4 levels, and C1-INH antigenic levels.[4,5] Patients with HAE type I have low C4 and C1-INH antigenic protein levels, along with low levels of functional C1-INH protein. Patients with HAE type II have low C4 and functional C1-INH protein level, with a normal or elevated C1-INH antigenic protein level. C1-INH replacement therapies are appropriate for both HAE type I and type II.

Patients with the third type of HAE called HAE with normal C1-INH (HAE nC1-INH), previously referred to as HAE type III, have normal C4 and C1-INH antigenic protein levels.[4] HAE nC1-INH is much less prevalent than HAE types I/II, and the exact cause of HAE nC1-INH has not been determined.[4,6] Pathogenic variants in the genes encoding for Factor XII (regulates bradykinin generation), angiopoietin-1 (involved in vascular permeability), and plasminogen have been associated with HAE nC1-INH; however, the majority of cases have unknown etiology. There are no randomized or controlled clinical trial data available with any therapy for use in HAE nC1-INH.[6-8]

Guidelines

Per the World Allergy Organization/European Academy of Allergy and Clinical Immunology guidelines (2017), all HAE type I/II attacks should be considered for acute treatment; treatment is mandatory for any attack potentially affecting the upper airway (HAE nC1-INH is not addressed within the scope of the guideline).[5] Attacks should be treated as early as possible. Self-administration at home facilitates earlier response. The guidelines recommend C1-INH products (Berinert, Cinryze, or Ruconest), Kalbitor® (ecallantide injection), or icatibant injection (Firazyr®, generics) as first-line treatment options. Androgens and anti-fibrinolytics are not effective as acute treatment. Patients should carry acute treatment with them at all times and should have enough supply on hand for treatment of two attacks. Other guidelines from the US Hereditary Angioedema Association Medical Advisory Board (2013), a practice parameter update from a Joint Task Force (2013), and an international and Canadian guideline (2019) have similar recommendations for acute treatment of HAE type I/II attacks.[6,9,11]

The decision to initiate long-term prophylaxis is individualized based on multiple factors and should be made by the patient and an HAE specialist.[6] C1-INH concentrate and Takhzyro™ (lanadelumab-flyo injection) are recognized as treatment options for long-term prophylaxis of HAE type I/II attacks.[5,6]

Androgens are not considered first-line and are contraindicated in certain groups (e.g., pregnancy, prepubescent children, androgen-dependent malignancy).[6] In other populations, the use of androgens for long-term prophylaxis may be considered as second-line but should be considered critically due to potential for adverse events. Therefore, guidelines note that androgens should not be used in patients who have a preference for alternative therapy and that patients should not be required to fail anabolic androgen therapy as a prerequisite to receiving prophylactic C1-INH or Takhzyro therapy.[6,9]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Berinert, Cinryze, and Ruconest. Because of the specialized skills required for evaluation and diagnosis of patients treated with these products, approval requires Berinert, Cinryze, or Ruconest to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Documentation: Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory records, and prescription claims records.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Berinert or Cinryze is recommended in those who meet the following criteria:

FDA-Approved Indications

13. Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Prophylaxis. Approve Berinert or Cinryze for the duration noted if the patient meets one of the following criteria (A or B):

A) Initial therapy. Approve for 1 year if the patient meets both of the following criteria (i and ii):

- **i.** Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):
  - **a)** Patient has low levels of functional C1-INH protein (< 50% of normal) at baseline, as defined by the laboratory reference values **[documentation required]**; AND
  - **b)** Patient has lower than normal serum C4 levels at baseline, as defined by the laboratory reference values **[documentation required]**; AND
- **ii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

B) Patients currently receiving Berinert or Cinryze prophylaxis. Approve for 1 year if the patient meets all of the following criteria (i, ii, and iii):

- **i.** Patient has a diagnosis of HAE type I or II **[documentation required]**; AND
- **ii.** According to the prescriber, the patient has had a favorable clinical response since initiating Berinert or Cinryze prophylactic therapy compared with baseline (i.e., prior to initiating prophylactic therapy); AND

  Note: Examples of favorable clinical response include decrease in HAE acute attack frequency, decrease in HAE attack severity, or decrease in duration of HAE attacks.
- **iii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

14. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Treatment of Acute Attacks.** Approve Berinert or Cinryze for the duration noted if the patient meets one of the following criteria (A or B):
    - **A)** Initial therapy. Approve for 1 year if the patient meets both of the following criteria (i and ii):
        - **i.** Patient has HAE type I or type II as confirmed by following criteria (a and b):
            - **a)** Patient has low levels of functional C1-INH protein (< 50% of normal) at baseline, as defined by the laboratory reference values **[documentation required]**; AND
            - **b)** Patient has lower than normal serum C4 levels at baseline, as defined by the laboratory reference values **[documentation required]**; AND
        - **ii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.
    - **B)** Patients who have treated previous acute HAE attacks with Berinert or Cinryze. Approve for 1 year if the patient meets all of the following criteria (i, ii, and iii):
        - **i.** Patient has a diagnosis of HAE type I or II **[documentation required]**; AND
        - **ii.** According to the prescriber, the patient has had a favorable clinical response with Berinert or Cinryze treatment; AND

          Note: Examples of favorable clinical response include decrease in the duration of HAE attacks, quick onset of symptom relief, complete resolution of symptoms, or decrease in HAE acute attack frequency or severity.
        - **iii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

II. Coverage of Ruconest is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Treatment of Acute Attacks.** Approve Ruconest for the duration noted if the patient meets one of the following criteria (A or B):
    - **A)** Initial therapy. Approve for 1 year if the patient meets both of the following criteria (i and ii):
        - **i.** Patient has HAE type I or type II as confirmed by following criteria (a and b):
            - **a)** Patient has low levels of functional C1-INH protein (< 50% of normal) at baseline, as defined by the laboratory reference values **[documentation required]**; AND
            - **b)** Patient has lower than normal serum C4 levels at baseline, as defined by the laboratory reference values **[documentation required]**; AND
        - **ii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.
    - **B)** Patients who have treated previous acute HAE attacks with Ruconest. Approve for 1 year if the patient meets all of the following criteria (i, ii, and iii):
        - **i.** Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND
        - **ii.** According to the prescriber, the patient has had a favorable clinical response with Ruconest treatment; AND

          Note: Examples of favorable clinical response include decrease in the duration of HAE attacks, quick onset of symptom relief, complete resolution of symptoms, or decrease in HAE acute attack frequency or severity.
        - **iii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Berinert, Cinryze, or Ruconest is not recommended in the following situations:

14. **Hereditary Angioedema (HAE) Prophylaxis (Ruconest ONLY).** Ruconest is not FDA-approved for prophylaxis of HAE attacks. A small (n = 32) Phase II, randomized, double-blind, placebo-controlled trial in adults and adolescents ≥ 13 years of age showed efficacy of Ruconest over placebo for reducing mean monthly rate of HAE attacks ($P < 0.0001$).[12] At this time, evidence is not sufficient to support Ruconest use for HAE prophylaxis. Note: This Condition Not Recommended for Approval does not apply to Berinert or Cinryze.

15. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Selected revision	**All indications:** Approval duration decreased to 1 year from 3 years. **Hereditary Angioedema (HAE) Prophylaxis (Ruconest ONLY):** Added to Conditions Not Recommended for Approval.	10/03/2018
Annual revision	**All indications**: "Prescribing physician" changed to "prescriber" throughout criteria.	08/07/2019
Annual revision	**All indications:** Examples of response to therapy moved to a note (previously these were listed in criteria).	08/26/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hereditary Angioedema – C1 Esterase Inhibitors (Subcutaneous) Prior Authorization Policy

- Haegarda® (C1 esterase inhibitor [human] for subcutaneous [SC] use – CSL Behring)

REVIEW DATE: 08/26/2020

OVERVIEW

Haegarda is a C1 esterase inhibitor (C1-INH) replacement therapy for hereditary angioedema (HAE).[1] It is a human plasma-derived C1-INH and is indicated for routine prophylaxis to prevent HAE attacks in adults and pediatric patients ≥ 6 years of age.[1]

Disease Overview

HAE due to C1-INH deficiency has two subtypes: HAE type I and HAE type II. HAE diagnosis can be confirmed by measuring functional C1-INH protein levels (usually < 50% of normal in patients with HAE), C4 levels, and C1-INH antigenic levels.[2,3] Patients with HAE type I have low C4 and C1-INH antigenic protein levels, along with low levels of functional C1-INH protein. Patients with HAE type II have low C4 and functional C1-INH protein level, with a normal or elevated C1-INH antigenic protein level. C1-INH replacement therapies are appropriate for both HAE type I and type II.

Patients with the third type of HAE called HAE with normal C1-INH (HAE nC1-INH), previously referred to as HAE type III, have normal C4 and C1-INH antigenic protein levels.[2] HAE nC1-INH is much less prevalent than HAE types I/II, and the exact cause of HAE nC1-INH has not been determined.[2,4] Pathogenic variants in the genes encoding for Factor XII (regulates bradykinin generation), angiopoietin-1 (involved in vascular permeability), and plasminogen have been associated with HAE nC1-INH; however, the majority of cases have unknown etiology. There are no randomized or controlled clinical trial data available with any therapy for use in HAE nC1-INH.[4-6]

Guidelines

According to international/Canadian guidelines (updated 2019), the decision to initiate long-term prophylaxis is individualized based on multiple factors and should be made by the patient and an HAE specialist.[4] C1-INH concentrate and Takhzyro™ (lanadelumab-flyo injection) are recognized as treatment options for long-term prophylaxis of HAE type I/II attacks.[3,4] Androgens are not considered first-line and are contraindicated in certain groups (e.g., pregnancy, prepubescent children, androgen-dependent malignancy).[4] In other populations, the use of androgens for long-term prophylaxis may be considered as second-line but should be considered critically due to potential for adverse events. Therefore, guidelines note that androgens should not be used in patients who have a preference for alternative therapy and that patients should not be required to fail anabolic androgen therapy as a prerequisite to receiving prophylactic C1-INH or Takhzyro therapy.[4,7]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Haegarda. Because of the specialized skills required for evaluation and diagnosis of patients treated with Haegarda, approval requires Haegarda to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Documentation: Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory records, and prescription claims records.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Haegarda is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Prophylaxis.** Approve Haegarda for the duration noted if the patient meets one of the following criteria (A or B):
   - **C)** Initial therapy. Approve for 1 year if the patient meets both of the following criteria (i and ii):
     - **i.** Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):
       - **a)** Patient has low levels of functional C1-INH protein (< 50% of normal) at baseline, as defined by the laboratory reference values **[documentation required]**; AND
       - **b)** Patient has lower than normal serum C4 levels at baseline, as defined by the laboratory reference values **[documentation required]**; AND
     - **ii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.
   - **D)** Patients currently receiving Haegarda prophylaxis. Approve for 1 year if the patient meets all of the following criteria (i, ii, and iii):
     - **i.** Patient has a diagnosis of HAE type I or II **[documentation required]**; AND
     - **ii.** According to the prescriber, the patient has had a favorable clinical response since initiating Haegarda prophylactic therapy compared with baseline (i.e., prior to initiating prophylactic therapy); AND

       Note: Examples of favorable clinical response include decrease in HAE acute attack frequency, decrease in HAE attack severity, or decrease in duration of HAE attacks.
     - **iii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Haegarda is not recommended in the following situations:

16. **Concomitant Use with Other HAE Prophylactic Therapies (e.g., Cinryze®, Takhzyro™).** Haegarda has not been studied in combination with other prophylactic therapies for HAE, and combination therapy for long-term prophylactic use is not recommended. Patients may use other medications, including Cinryze, for treatment of acute HAE attacks, and for short-term (procedural) prophylaxis.

17. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Selected revision	**Concomitant use with other HAE prophylactic therapies:** Added to conditions not recommended for approval. **All Indications:** Approval duration decreased to 1 year from 3 years.	10/03/2018
Annual revision	**All Indications:** "Prescribing physician" changed to "prescriber" throughout policy.	08/07/2019
Annual revision	Examples of response to therapy moved to a note (previously these were listed in criteria).	08/26/2020
DEU update	**01/25/2021:** No changes to criteria. The Overview section was updated to include expanded indication in pediatric patients.	NA

PRIOR AUTHORIZATION POLICY

POLICY: Hereditary Angioedema – Icatibant (Firazyr) Prior Authorization Policy
- Firazyr® (icatibant injection for subcutaneous use – Shire/Takeda)
- Icatibant injection for subcutaneous use – various

REVIEW DATE: 08/19/2020

OVERVIEW

Icatibant (Firazyr, generics) is a synthetic decapeptide that is indicated for the treatment of acute hereditary angioedema (HAE) attacks in adults ≥ 18 years of age.[1] Icatibant is a competitive bradykinin B2 receptor antagonist with an affinity similar to bradykinin. Bradykinin is a vasodilator which is likely responsible for the characteristic HAE symptoms of localized swelling, inflammation and pain. By preventing the binding of bradykinin to its receptor, icatibant treats the clinical symptoms of an acute HAE attack.

Disease Overview

HAE due to C1 esterase inhibitor (C1-INH) deficiency has two subtypes: HAE type I and HAE type II. HAE diagnosis can be confirmed by measuring functional C1-INH protein levels (usually < 50% of normal in patients with HAE), C4 levels, and C1-INH antigenic levels.[2,3] Patients with HAE type I have low C4 and C1-INH antigenic protein levels, along with low levels of functional C1-INH protein. Patients with HAE type II have low C4 and functional C1-INH protein level, with a normal or elevated C1-INH antigenic protein level. C1-INH replacement therapies are appropriate for both HAE type I and type II.

Patients with the third type of HAE called HAE with normal C1-INH (HAE nC1-INH), previously referred to as HAE type III, have normal C4 and C1-INH antigenic protein levels.[2] HAE is much less prevalent

than HAE types I/II, and the exact cause of HAE nC1-INH has not been determined.[2,4] Pathogenic variants in the genes encoding for Factor XII (regulates bradykinin generation), angiopoietin-1 (involved in vascular permeability), and plasminogen have been associated with HAE nC1-INH; however, the majority of cases have unknown etiology. There are no randomized or controlled clinical trial data available with any therapy for use in HAE nC1-INH.[4-6]

Guidelines

Per the World Allergy Organization/European Academy of Allergy and Clinical Immunology guidelines (2017), all HAE type I/II attacks should be considered for acute treatment; treatment is mandatory for any attack potentially affecting the upper airway (HAE nC1-INH is not addressed within the scope of the guideline).[3] Attacks should be treated as early as possible. Self-administration at home facilitates earlier response. The guidelines recommend C1-INH products, Kalbitor® (ecallantide for subcutaneous injection), or icatibant as first-line treatment options. Androgens and antifibrinolytics are not effective as acute treatment. Patients should carry acute treatment with them at all times and should have enough supply on hand for treatment of two attacks. Other guidelines from the US Hereditary Angioedema Association Medical Advisory Board (2013), a practice parameter update from a Joint Task Force (2013), and an international and Canadian guideline (2019) have similar recommendations regarding acute treatment of HAE type I/II attacks.[4,7,8]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of icatibant. Because of the specialized skills required for evaluation and diagnosis of patients treated with icatibant, approval requires it to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Documentation: Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory records, and prescription claims records.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of icatibant is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency (Type I or Type II) – Treatment of Acute Attacks.** Approve for the duration noted if the patient meets one of the following criteria (A or B):
   - **A)** Initial therapy. Approve for 1 year if the patient meets both of the following criteria (i and ii):
     - **i.** Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):
       - **a)** Patient has low levels of functional C1-INH protein (< 50% of normal) at baseline, as defined by the laboratory reference values **[documentation required]**; AND
       - **b)** Patient has lower than normal serum C4 levels at baseline, as defined by the laboratory reference values **[documentation required]**; AND
     - **ii.** The medication is prescribed by, or in consultation with, an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

B) Patient who has treated previous acute HAE attacks with icatibant (Firazyr). Approve for 1 year if the patient meets all of the following criteria (i, ii, and iii):

- **i.** Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND
- **ii.** According to the prescriber, the patient has had a favorable clinical response (e.g., decrease in the duration of HAE attacks, quick onset of symptom relief, complete resolution of symptoms, decrease in HAE acute attack frequency or severity) with icatibant treatment; AND
- **iii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of icatibant is not recommended in the following circumstances:

18. Hereditary Angioedema (HAE) Prophylaxis. Data are not available and icatibant is not indicated for prophylaxis of HAE attacks.

19. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Early annual revision	**All Indications:** Approval duration decreased to 1 year from 3 years.	10/03/2018
Early annual revision	Generic icatibant added to policy.	07/24/2019
Annual revision	"Prescribing physician" updated to "prescriber" throughout criteria.	08/19/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hereditary Angioedema – Kalbitor Prior Authorization Policy

- Kalbitor® (ecallantide injection for subcutaneous use – Dyax)

REVIEW DATE: 08/26/2020

OVERVIEW

Kalbitor, a plasma kallikrein inhibitor, is indicated for the treatment of acute attacks of hereditary angioedema (HAE) in patients ≥ 12 years of age.[1] Potentially serious hypersensitivity reactions, including anaphylaxis, have occurred in patients treated with Kalbitor. Kalbitor should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and HAE.

Disease Overview

HAE due to C1 esterase inhibitor (C1-INH) deficiency has two subtypes: HAE type I and HAE type II. HAE diagnosis can be confirmed by measuring functional C1-INH protein levels (usually < 50% of normal in patients with HAE), C4 levels, and C1-INH antigenic levels.[2,3] Patients with HAE type I have low C4 and C1-INH antigenic protein levels, along with low levels of functional C1-INH protein. Patients with HAE type II have low C4 and functional C1-INH protein level, with a normal or elevated C1-INH antigenic protein level. C1-INH replacement therapies are appropriate for both HAE type I and type II.

Patients with the third type of HAE called HAE with normal C1-INH (HAE nC1-INH), previously referred to as HAE type III, have normal C4 and C1-INH antigenic protein levels.[2] HAE nC1-INH is much less

prevalent than HAE types I/II, and the exact cause of HAE nC1-INH has not been determined.[2,4] Pathogenic variants in the genes encoding for Factor XII (regulates bradykinin generation), angiopoietin-1 (involved in vascular permeability), and plasminogen have been associated with HAE nC1-INH; however, the majority of cases have unknown etiology. There are no randomized or controlled clinical trial data available with any therapy for use in HAE nC1-INH.[4-6]

Guidelines

Per the World Allergy Organization/European Academy of Allergy and Clinical Immunology guidelines (2017), all HAE type I/II attacks should be considered for acute treatment; treatment is mandatory for any attack potentially affecting the upper airway (HAE nC1-INH is not addressed within the scope of the guideline).[3] Attacks should be treated as early as possible. Self-administration at home facilitates earlier response. The guidelines recommend C1-INH products, Kalbitor, or icatibant injection (Firazyr®, generics) as first-line treatment options. Androgens and anti-fibrinolytics are not effective as acute treatment. Patients should carry acute treatment with them at all times and should have enough supply on hand for treatment of two attacks. Other guidelines from the US Hereditary Angioedema Association Medical Advisory Board (2013), a practice parameter update from a Joint Task Force (2013), and an international and Canadian guideline (2019) have similar recommendations for acute treatment of HAE type I/II attacks.[4,7,8]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Kalbitor. Because of the specialized skills required for the evaluation and diagnosis of patients treated with Kalbitor, approval requires Kalbitor to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Documentation: Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory records, and prescription claims records.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kalbitor is recommended in those who meet the following criteria:

FDA-Approved Indications

2. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Treatment of Acute Attacks.** Approve Kalbitor for the duration noted if the patient meets one of the following criteria (A or B):
   - **C)** Initial therapy. Approve for 1 year if the patient meets both of the following criteria (i and ii):
     - **i.** Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):
       - **a)** Patient has low levels of functional C1-INH protein (< 50% of normal) at baseline, as defined by the laboratory reference values **[documentation required]**; AND
       - **b)** Patient has lower than normal serum C4 levels at baseline, as defined by the laboratory reference values **[documentation required]**; AND
     - **ii.** The medication is prescribed by, or in consultation with, an allergist/immunologist or a physician that specializes in the treatment of HAE or related disorders.

D) Patient who has treated previous acute HAE attacks with Kalbitor. Approve for 1 year if the patient meets all of the following criteria (i, ii, and iii):

i. Patient has a diagnosis of HAE type I or II **[documentation required]**; AND

ii. According to the prescriber, the patient has had a favorable clinical response with Kalbitor treatment; AND

Note: Examples of favorable clinical response include decrease in the duration of HAE attacks, quick onset of symptom relief, complete resolution of symptoms, or decrease in HAE acute attack frequency or severity.

iii. The medication is prescribed by or in consultation with an allergist/immunologist or a physician that specializes in the treatment of HAE or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kalbitor is not recommended in the following situations:

5. **Hereditary Angioedema (HAE) Prophylaxis.** Data are not available and Kalbitor is not indicated for the prophylaxis of HAE attacks.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
Early annual revision	**All Indications:** Approval duration decreased to 1 year from 3 years.	10/03/2018
Annual revision	**All Indications:** "Prescribing physician" changed to "prescriber" throughout policy.	08/07/2019
Annual revision	Examples of response to therapy moved to a note (previously these were listed in criteria).	08/26/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hereditary Angioedema – Orladeyo Prior Authorization Policy
- Orladeyo™ (berotralstat capsules – Biocryst)

REVIEW DATE: 12/09/2020

OVERVIEW

Orladeyo, an inhibitor of plasma kallikrein, is indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients ≥ 12 years of age.[1]

Disease Overview

HAE due to C1 esterase inhibitor (C1-INH) deficiency has two subtypes: HAE type I and HAE type II. HAE diagnosis can be confirmed by measuring functional C1-INH protein levels (usually < 50% of normal in patients with HAE), C4 levels, and C1-INH antigenic levels.[2,3] Patients with HAE type I have low C4 and C1-INH antigenic protein levels, along with low levels of functional C1-INH protein. Patients with HAE type II have low C4 and functional C1-INH protein level, with a normal or elevated C1-INH antigenic protein level. C1-INH replacement therapies are appropriate for both HAE type I and type II.

Patients with the third type of HAE called HAE with normal C1-INH (HAE nC1-INH), previously referred to as HAE type III, have normal C4 and C1-INH antigenic protein levels.[2] HAE nC1-INH is much less prevalent than HAE types I/II, and the exact cause of HAE nC1-INH has not been determined.[2,4] Pathogenic variants in the genes encoding for Factor XII (regulates bradykinin generation), angiopoietin-1 (involved in vascular permeability), and plasminogen have been associated with HAE nC1-INH; however, the majority of cases have unknown etiology. There are no randomized or controlled clinical trial data available with any therapy for use in HAE nC1-INH.[4-6]

Guidelines

Orladeyo is not yet addressed in guideline recommendations, although positive Phase III data are recognized in 2020 guidelines from the US HAE Association Medical Advisory Board.[8] Per guidelines, the decision to initiate long-term prophylaxis is individualized based on multiple factors and should be made by the patient and an HAE specialist.[4,8] C1-INH concentrate and Takhzyro™ (lanadelumab-flyo subcutaneous injection) are recognized as first-line treatment options for long-term prophylaxis of HAE type I/II attacks.[3,4,8] Androgens are not considered first-line and are contraindicated in certain groups (e.g., pregnancy, prepubescent children, androgen-dependent malignancy).[4] In other populations, the use of androgens for long-term prophylaxis may be considered as second-line but should be considered critically due to potential for adverse events. Therefore, guidelines note that androgens should not be used in patients who have a preference for alternative therapy and that patients should not be required to fail anabolic androgen therapy as a prerequisite to receiving prophylactic C1-INH or Takhzyro therapy.[4,7] Of note, long-term prophylaxis for patients with HAE with normal C1-INH has not been studied in a randomized, placebo-controlled trial; hormonal therapy and antifibrinolytics are generally used for prophylaxis in this scenario.[8]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Orladeyo. Because of the specialized skills required for evaluation and diagnosis of patients with this condition, approval requires Orladeyo to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Documentation: Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory records, and prescription claims records.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Orladeyo is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Prophylaxis.** Approve Orladeyo for the duration noted if the patient meets one the following criteria (A or B):
   - **E)** Initial therapy. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient is ≥ 12 years of age; AND
     - **ii.** Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):
       - **a)** Patient has low levels of functional C1-INH protein (< 50% of normal) at baseline, as defined by the laboratory reference values **[documentation required]**; AND
       - **b)** Patient has lower than normal serum C4 levels at baseline, as defined by the laboratory reference values **[documentation required]**; AND
     - **iii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.
   - **F)** Patient is currently receiving Orladeyo. Approve for 1 year if the patient meets all of the following criteria (i, ii, iii, and iv):
     - **i.** Patient is ≥ 12 years of age; AND
     - **ii.** Patient has a diagnosis of HAE type I or II **[documentation required]**; AND
     - **iii.** According to the prescriber, the patient has had a favorable clinical response since initiating Orladeyo prophylactic therapy compared with baseline (i.e., prior to initiating prophylactic therapy); AND
       Note: Examples of favorable clinical response include decrease in HAE acute attack frequency, decrease in HAE attack severity, or decrease in duration of HAE attacks.
     - **iv.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Orladeyo is not recommended in the following situations:

20. **Concomitant Use with Other HAE Prophylactic Therapies (e.g., Cinryze®, Haegarda®, Takhzyro).** Orladeyo has not been studied in combination with other prophylactic therapies for HAE, and combination therapy for long-term prophylactic use is not recommended. Patients may use other medications, including Cinryze, for on-demand treatment of acute HAE attacks, and for short-term (procedural) prophylaxis.

21. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Orladeyo™ capsules [prescribing information]. Durham, NC: Biocryst; December 2020.
2. Bowen T, Cicardi M, Farkas H, et al. 2010 international consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Ann Allergy Asthma Immunol*. 2010;6:24.
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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/09/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hereditary Angioedema – Takhzyro Prior Authorization Policy

- Takhzyro™ (lanadelumab-flyo for subcutaneous injection – Shire/Takeda)

REVIEW DATE: 08/26/2020

OVERVIEW

Takhzyro, a human monoclonal antibody inhibitor of plasma kallikrein, is indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients ≥ 12 years of age.[1]

Disease Overview

HAE due to C1 esterase inhibitor (C1-INH) deficiency has two subtypes: HAE type I and HAE type II. HAE diagnosis can be confirmed by measuring functional C1-INH protein levels (usually < 50% of normal in patients with HAE), C4 levels, and C1-INH antigenic levels.[2,3] Patients with HAE type I have low C4 and C1-INH antigenic protein levels, along with low levels of functional C1-INH protein. Patients with HAE type II have low C4 and functional C1-INH protein level, with a normal or elevated C1-INH antigenic protein level. C1-INH replacement therapies are appropriate for both HAE type I and type II.

Patients with the third type of HAE called HAE with normal C1-INH (HAE nC1-INH), previously referred to as HAE type III, have normal C4 and C1-INH antigenic protein levels.[2] HAE nC1-INH is much less prevalent than HAE types I/II, and the exact cause of HAE nC1-INH has not been determined.[2,4] Pathogenic variants in the genes encoding for Factor XII (regulates bradykinin generation), angiopoietin-1 (involved in vascular permeability), and plasminogen have been associated with HAE nC1-INH; however, the majority of cases have unknown etiology. There are no randomized or controlled clinical trial data available with any therapy for use in HAE nC1-INH.[4-6]

Guidelines

According to international/Canadian guidelines (updated 2019), the decision to initiate long-term prophylaxis is individualized based on multiple factors and should be made by the patient and an HAE specialist.[4] C1-INH concentrate and Takhzyro are recognized as treatment options for long-term prophylaxis of HAE type I/II attacks.[3,4] Androgens are not considered first-line and are contraindicated in certain groups (e.g., pregnancy, prepubescent children, androgen-dependent malignancy).[4] In other populations, the use of androgens for long-term prophylaxis may be considered as second-line but should be considered critically due to potential for adverse events. Therefore, guidelines note that androgens should not be used in patients who have a preference for alternative therapy and that patients should not be required to fail anabolic androgen therapy as a prerequisite to receiving prophylactic C1-INH or Takhzyro therapy.[4,7]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Takhzyro. Because of the specialized skills required for evaluation and diagnosis of patients with this condition, approval requires Takhzyro to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Documentation: Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory records, and prescription claims records.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Takhzyro is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Prophylaxis.** Approve Takhzyro for the duration noted if the patient meets one the following criteria (A or B):
   - **G)** Initial therapy. Approve for 1 year if the patient meets both of the following criteria (i and ii):
     - **i.** Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):
       - **a)** Patient has low levels of functional C1-INH protein (< 50% of normal) at baseline, as defined by the laboratory reference values **[documentation required]**; AND
       - **b)** Patient has lower than normal serum C4 levels at baseline, as defined by the laboratory reference values **[documentation required]**; AND
     - **ii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.
   - **H)** Patients currently receiving Takhzyro prophylaxis. Approve for 1 year if the patient meets all of the following criteria (i, ii, and iii):
     - **i.** Patient has a diagnosis of HAE type I or II **[documentation required]**; AND
     - **ii.** According to the prescriber, the patient has had a favorable clinical response since initiating Takhzyro prophylactic therapy compared with baseline (i.e., prior to initiating prophylactic therapy); AND

       Note: Examples of favorable clinical response include decrease in HAE acute attack frequency, decrease in HAE attack severity, or decrease in duration of HAE attacks.

iii. The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Takhzyro is not recommended in the following situations:

22. Concomitant Use with Other HAE Prophylactic Therapies (e.g., Cinryze®, Haegarda®). Takhzyro has not been studied in combination with other prophylactic therapies for HAE, and combination therapy for long-term prophylactic use is not recommended. Patients may use other medications, including Cinryze, for on-demand treatment of acute HAE attacks, and for short-term (procedural) prophylaxis.

23. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New policy	--	08/24/2018
Selected revision	"Concomitant use with other HAE prophylactic therapies" added to conditions not recommended for approval. Approval duration changed to 1 year.	09/12/2018
Annual revision	**All Indications:** "Prescribing physician" changed to "prescriber" throughout policy.	08/07/2019
Annual revision	Examples of response to therapy moved to a note (previously these were listed in criteria).	08/26/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hetlioz Prior Authorization Policy

- Hetlioz™ (tasimelteon capsules – Vanda Pharmaceuticals)
- Hetlioz LQ™ (tasimelteon oral suspension – Vanda Pharmaceuticals)

REVIEW DATE: 01/27/2021

OVERVIEW

Hetlioz/Hetlioz LQ, melatonin receptor agonists, are indicated for the following uses:[1]

- Hetlioz is indicated for the treatment of:
  - **i. Non-24-Hour Sleep-Wake Disorder** (Non-24).
  - **ii. Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS)**, in patients ≥ 16 years of age.
- Hetlioz LQ is indicated for the treatment of **nighttime sleep disturbances in SMS** in patients 3 to 15 years of age.

Disease Overview

Non-24 is a chronic, circadian rhythm disorder that is due to the misalignment of the endogenous master body clock to the 24-hour day which disrupts the sleep-wake cycle and commonly is thought to be caused by the failure of light to reach the suprachiasmatic nuclei. Patients who are completely blind are particularly susceptible to this condition and the prevalence of non-entrained rhythms in totally blind patients is 55% to 70%.[2-7] It has been estimated that of the 1.3 million people in the US who are blind, 10% of people have no light perception, a risk factor for this disorder,

and reports suggest that as many as one-half to three-quarters of totally blind patients have Non-24, which is approximately 65,000 to 95,000 Americans.[6] Patients can be diagnosed using circadian phase markers (e.g., measurement of urinary melatonin levels, dim light melatonin onset [assessed in blood or saliva], or assessing core body temperature).[2,7-8] Alternative forms of diagnosis include actigraphy and assessment of sleep logs (sleep diaries).[2,7-8] Actigraphy is a non-invasive method of monitoring human rest and activity cycles and involves the use of a portable device to document movement. Other reviews confirm these diagnostic methods.[7-8]

SMS is a rare disorder identified by an array of physical, neurobehavioral, and developmental characteristics.[14] In the United States, the incidence is estimated to be 1 in 15,000 to 25,000 people in the general population. Predominately cases of SMS are related to either a deletion or mutation in the *RAI1* gene. It affects males and females equally and is found in ethnic groups all over the world. Common symptoms comprise of distinctive facial features, skeletal malformations, varying degrees of intellectual disability, speech and motor delays, sleep disturbances, and self-injurious/attention-seeking behaviors. Sleep disturbances start as early as one year of age and continue into adulthood and include shortened sleep cycles with multiple awakenings during the night, early morning arousal from sleep, and increased somnolence during daytime hours. Inability to achieve a normal sleeping pattern appears to aggravate behavioral issues such as impulsivity, aggression, hyperactivity and frequent temper tantrums. Sleep issues in SMS have been attributed to a primary disturbance of the circadian clock disruption and instabilities in melatonin secretion. Physical traits such as muscle weakness, obesity-related breathing difficulties, and facial composition can be underlying factors that affect sleep.

Clinical Efficacy

The efficacy of Hetlioz for Non-24 was established in two Phase III pivotal studies involving totally blind patients who reported no light perception with Non-24 for up to 6 months and evaluated the effects of Hetlioz withdrawal.[1-2] Patients were ≥ 18 years of age and could be enrolled if they had a non-24-hour tau of 24.25 hours or longer as calculated from the rhythm of urinary 6-sulphatoxymelatonin (aMT6s), the major melatonin metabolite. At Month 1, more patients receiving Hetlioz (20%, n = 8/40) were entrained compared with patients randomized to placebo (3%, n = 1/38) [P = 0.0171].[2] Entrainment is defined as the synchronization of the circadian rhythm of the body to the 24-hour day.[2-5] In the Hetlioz group, 29% of patients (n = 12) met responder criteria, defined as patients with both a ≥ 45 minute increase in nighttime sleep and a ≥ 45 minute decrease in daytime nap time, compared with 12% of patients (n = 5) who received placebo (time of endpoint assessment not stated).[1] During the withdrawal period of the trial, which lasted 8 weeks, 90% of patients who continued Hetlioz (n = 9/10) remained entrained compared with 20% of patients randomized to receive placebo (n = 2/10) [P = 0.0026].[2-3]

The role of Hetlioz and Hetlioz LQ for nighttime sleep disturbances in SMS is extremely limited.[1] Data supporting benefits with these agents are lacking and underwhelming. The pivotal trial for SMS is unpublished, included very few patients, and was relatively short-term; this condition would likely require long-term therapy. Only one of the two primary efficacy endpoints was statistically significant after controlling for multiple comparisons.

Guidelines

In 2015, clinical practice guidelines were published by the American Academy of Sleep Medicine (AASM) that addresses non-24-hour sleep-wake rhythm disorder (N24SWD).[5] The guidelines state the N24SWD occurs when the hypothalamic circadian pacemaker does not entrain (synchronize) to the 24 hour day. Patients may experience periodic nighttime insomnia and daytime somnolence as the circadian rhythms of sleep propensity and alertness drift in and out of synchrony with the usual 24-hour day. The condition mainly occurs in patients who are blind. The Task Force state that there is no evidence to support the use of sleep-promoting medications in patients with N24SWD. Data suggests that melatonin entrainment occurs with melatonin at a greater rate than placebo and melatonin can be an effective treatment for N24SWD. The Task Force recommendation was that clinicians use strategically timed melatonin for the treatment of N24SWD in adults who are blind (versus no treatment). There are insufficient data to support use of melatonin among sighted patients with N24SWD (versus no treatment).

The Parents and Researchers Interested in Smith-Magenis Syndrome (PRISMS) created medical management guidelines for the diagnosis, treatment of manifestations, and ongoing surveillance of SMS.[15] The guidelines do not address Hetlioz/Hetlioz LQ. Multidisciplinary treatment with multimodal options provided by practitioners from different disciplines are recommended. The guidelines recognize sleep management is a challenge and no well-controlled treatment trials have been reported. The first suggestion is to incorporate a good sleep routine (e.g., consistent bedtime and bedtime routine, quiet/non-stimulating activities, use of white noise or a rhythmic sound, and

a comfortably cool/dark room). Concerns for sleep apnea should be addressed. Melatonin is endorsed as monotherapy for sleep management. The concomitant use of a morning beta-blocker (acebutolol) with an evening dose of melatonin for 6 to 8 weeks could be beneficial to restore circadian plasma melatonin rhythmicity, decrease daytime sleepiness, improve daytime behavior, and enhance sleep in children with SMS.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Hetlioz/Hetlioz LQ. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Hetlioz/Hetlioz LQ as well as the monitoring required for adverse events and long-term efficacy, approval requires Hetlioz/Hetlioz LQ to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Hetlioz capsules are recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Non-24-Hour Sleep Wake Disorder (Non-24).** Approve for the duration noted if the patient meets one of the following conditions (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets all of the following criteria (i, ii, iii, iv, and v):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient is totally blind with no perception of light; AND
     - **iii.** Diagnosis of Non-24 is confirmed by meeting ONE of the following conditions (a or b):
       - **a)** Assessment of at least one physiologic circadian phase marker; OR
         Note: Examples of physiologic circadian phase markers include measurement of urinary melatonin levels, dim light melatonin onset (as measured in blood or saliva), and assessment of core body temperature.
       - **b)** If assessment of at least one physiologic circadian phase marker cannot be done, the diagnosis must be confirmed by actigraphy performed for ≥ 1 week plus evaluation of sleep logs recorded for ≥ 1 month; AND
     - **iv.** Patient meets BOTH of the conditions (a and b):
       - **a)** Patient has received at least 6 months of continuous therapy (i.e., 6 consecutive months of daily treatment) with melatonin under the guidance of a physician who specializes in the treatment sleep disorders; AND
       - **b)** Patient had inadequate efficacy with melatonin therapy according to the prescriber; AND
         Note: Examples of efficacy with melatonin therapy include entrainment, clinically meaningful or significant increases in nighttime sleep, and clinically meaningful or significant decreases in daytime sleep.
     - **v.** The medication is prescribed by, or in consultation with, a physician who specializes in the treatment of sleep disorders.
   - **B)** Patient is Currently Receiving Hetlioz. Approve for 1 year if the patient meets all of the following criteria (i, ii, iii, iv, v, and vi):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient is totally blind with no perception of light; AND
     - **iii.** Patient meets both of the conditions (a and b):
       - **a)** Patient has received at least 6 months of continuous therapy (i.e., 6 consecutive months of daily treatment) with melatonin under the guidance of a physician who specializes in the treatment sleep disorders; AND
       - **b)** Patient had inadequate efficacy with melatonin therapy according to the prescriber; AND

Note: Examples of efficacy with melatonin therapy include entrainment, clinically meaningful or significant increases in nighttime sleep, and clinically meaningful or significant decreases in daytime sleep.

iv. Patient meets both of the conditions (a and b):

a) Patient has received at least 6 months of continuous therapy (i.e., 6 consecutive months of daily treatment) with Hetlioz under the guidance of a physician who specializes in the treatment of sleep disorders; AND

Note: Patients who have not received at least 6 months of continuous Hetlioz therapy, or if the therapy has not been continuous (i.e., 6 consecutive months of daily treatment), should follow criteria 1 (initial therapy).

b) Patient has achieved adequate results with Hetlioz therapy according to the prescriber; AND

Note: Examples of adequate results with Hetlioz therapy include entrainment, clinically meaningful or significant increases in nighttime sleep, clinically meaningful or significant decreases in daytime sleep.

v. The medication is prescribed by, or in consultation with, a physician who specializes in the treatment of sleep disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Hetlioz/Hetlioz LQ is not recommended in the following situations:

24. Insomnia, Primary. Many other agents are available.[9] Only limited data have investigated use of Hetlioz in patients with primary insomnia.[10] Further data are needed to establish the safety and efficacy of Hetlioz.

25. Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS). Efficacy data for Hetlioz/Hetlioz LQ for nighttime sleep disturbances in SMS supporting benefits with these agents are lacking and underwhelming.[1] The pivotal trial included few patients and is unpublished (limited to the prescribing information).

26. Ramelteon tablets (Rozerem™, generics), Concomitant Therapy. Ramelteon tablets, a melatonin receptor agonist, are indicated for the treatment of insomnia characterized by difficulty with sleep onset.[11] The safety and efficacy of concomitant use of ramelteon tablets and Hetlioz have not been studied and it is suspected that the adverse events with use of these agents with a similar mechanism of action taken together may be additive (e.g., central nervous system effects [somnolence], hepatic impairment). Rozerem has not been studied in Non-24. In the clinical trials with Hetlioz, patients were not permitted to use medications that could interfere with the assessment of circadian rhythms.

27. Sedative Hypnotic Medications or Other Medications for Insomnia or Other Sleep-Related Disorders, Concomitant Therapy (e.g., benzodiazepines [triazolam, temazepam], nonbenzodiazepine hypnotics [e.g., zolpidem, zaleplon], chloral hydrate). There are no data to support the safety and efficacy of hypnotic medications in patients with Non-24.[5] Also, there are no data to determine the safety and efficacy of Hetlioz when used with other sedative hypnotic medications or other medications for insomnia or sleep-related disorders.[12]

28. Sleep-Related Disorders, Other Types (e.g. shift work disorder, jet lag disorder, advanced sleep phase disorder, delayed sleep phase disorder, irregular sleep-wake rhythm disorder). A published investigation details a Phase II study (n = 29) and a Phase III study (n = 411) assessing Hetlioz treatment in adults with transient insomnia associated with shifted sleep and wake time.[13] Further studies are needed to establish the efficacy and safety of Hetlioz in patients with other types of sleep-related disorders.

29. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	04/17/2019
Annual Revision	No criteria changes.	04/15/2020
Early Annual Revision	Hetlioz LQ was added to the policy. **Non-24-Hour Sleep Wake Disorder (Non-24).** Initial Therapy: For the exception applying to patients who did not achieve adequate results with melatonin therapy, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician) and "did not achieve adequate results" was changed to "had inadequate efficacy". The examples of physiologic circadian phase markers and adequate results with melatonin therapy were moved to a Note (previously listed as examples within the criteria). Patient Currently Receiving Hetlioz: Requirement that the patient has previously tried melatonin for at least 6 months of continuous therapy with inadequate efficacy was added to the criteria. For the exception applying to patients who achieved adequate results with Hetlioz therapy, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). The examples of adequate results with Hetlioz therapy were moved to a Note (previously listed as examples within the criteria). **Nighttime Sleep Disturbances in Smith-Magenis Syndrome:** This new indication was added to the "Conditions Not Recommended for Approval" section of the policy.	01/27/2021

PRIOR AUTHORIZATION POLICY

POLICY: Homozygous Familial Hypercholesterolemia – Evkeeza Prior Authorization Policy

- Evkeeza™ (evinacumab-dgnb injection for intravenous use – Regeneron)

REVIEW DATE: 02/17/2021; updated 02/24/2021

OVERVIEW

Evkeeza, an angiopoietin-like 3 inhibitor, is indicated as an adjunct to other low-density lipoprotein cholesterol (LDL-C) lowering therapies for the treatment of homozygous familial hypercholesterolemia (HoFH) in adults and pediatric patients ≥ 12 years of age.[1]

In the pivotal trial that led to approval of Evkeeza, patients were receiving additional medications to lower LDL-C levels such as statins (94% [77% of patients at high-intensity statin doses]), a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor (77%), ezetimibe (75%), and Juxtapid® (lomitapide capsules). Although some Phase II data are available,[3] the safety and effectiveness of Evkeeza have not been established in patients with other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH).[1] The effects of Evkeeza on cardiovascular morbidity and mortality have not been determined.

Disease Overview

Familial hypercholesterolemias, which include HeFH and HoFH, encompass a group of genetic defects that cause severe elevations in LDL-C levels, as well as other lipid parameters.[4,5] HoFH impacts approximately 1 in 300,000 to 1,000,000 persons. The condition is most commonly due to impaired functionality of the low-density lipoprotein (LDL) receptor which leads to a low or absence of clearance of LDL-C from the circulation. Currently known causes of familial hypercholesterolemia include mutations in the LDL receptor, apolipoprotein B (apo B), or proprotein convertase subtilisin kexin type 9 (PCSK9) genes. Patients with familial hypercholesterolemia may have physical findings such as tendon or cutaneous xanthomas, which may occur in childhood. Individuals with familial hypercholesterolemia are at very high risk of atherosclerotic cardiovascular disease (ASCVD) at a premature age. Most guidelines recommended LDL-C targets of < 100 mg/dL for adults and < 70 mg/dL for adults with ASCVD or other risk factors. Statins are the initial treatment for familial hypercholesterolemia. For patients with HoFH, high-intensity statin therapy is recommended, with ezetimibe added as well. Therapy with a PCSK9 inhibitor (e.g., Repatha® [evolocumab injection for subcutaneous use]) is usually the next step. Other non-statin therapies can be considered (e.g., colesevelam tablets or oral suspension, niacin). Combination therapy is required for most patients. LDL apheresis is recommended in certain circumstances. Patients with HoFH should be managed by a lipid specialist. Table 1 provides some of the diagnostic criteria to establish a diagnosis of HoFH. The diagnosis of HoFH can be done by genetic or clinical criteria.

Table 1. Criteria for the Diagnosis of HoFH.[5]

- Genetic confirmation of two mutant alleles at the LDLR, Apo B, PCSK9 or LDLRAP1 gene locus; OR
- An untreated LDL-C > 500 mg/dL* or treated LDL-C > 300 mg/dL* together with either 1) cutaneous or tendon xanthoma before the age of 10 years OR 2) untreated elevated LDL-C levels consistent with heterozygous FH in both parents.

HoFH – Homozygous familial hypercholesterolemia; LDLR – Low-density lipoprotein receptor; Apo B – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9; LDLRAP1 – Low-density lipoprotein receptor adaptor protein 1; LDL-C – Low-density lipoprotein cholesterol; * These cited LDL-C levels are only indicative and lower levels, especially in children or in untreated patients do not exclude HoFH; FH – Familial hypercholesterolemia.

Guidelines

Evkeeza is not addressed in guidelines. Several guidelines provide strategies for managing familial hypercholesterolemia, including HoFH.

- **American Heart Association/American College of Cardiology [2018]**: In patients with severe primary hypercholesterolemia (LDL-C ≥ 190 mg/dL) begin high-intensity statin therapy.[6] If the LDL-C levels remains ≥ 100 mg/dL, add ezetimibe. If the LDL-C remains ≥ 100 mg/dL on this regimen, consider a PCSK9 inhibitor if the patient has multiple risk factors that increase the risk of ASCVD. Other therapies can also be used (e.g., bile acid sequestrants).
- **European Atherosclerosis Society (2014):** A position paper by this organization recommends lipid-lowering therapy be initiated as soon as possible with LDL-C targets for HoFH of < 100 mg/dL in adults or < 70 mg/dL in adults with clinical ASCVD.[5] Statins are a mainstay of therapy

and are often used in combination with other agents such as ezetimibe. Other agents can be alternatives as well (e.g., Juxtapid® [lomitapide capsules]). Lipoprotein apheresis may also be considered.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Evkeeza. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Evkeeza, as well as the monitoring required for adverse events and long-term efficacy, approval requires Evkeeza to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: None required.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Evkeeza is recommended in those who meet the following criteria:

FDA-Approved Indication

70. Homozygous Familial Hypercholesterolemia. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):

43. Patient is ≥ 12 years of age; AND

44. Patient meets one of the following (i, ii or iii):

i. Patient has had genetic confirmation of two mutant alleles at the low-density lipoprotein receptor (LDLR), apolipoprotein B (apo B), proprotein convertase subtilisin kexin type 9 (PCSK9) or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene locus; OR

ii. Patient has an untreated low-density lipoprotein cholesterol (LDL-C) level > 500 mg/dL AND meets one of the following (a or b); OR

Note: Untreated refers to prior to therapy with any antihyperlipidemic agent.

a) Patient had clinical manifestations of homozygous familial hypercholesterolemia (HoFH) before the age of 10 years; OR

Note: Clinical manifestations of HoFH are cutaneous xanthomas, tendon xanthomas, acrus cornea, tuberous xanthomas, or xanthelasma.

b) Both parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia (HeFH); OR

Note: An example of HeFH in both parents would be if both had an untreated LDL-C level ≥ 190 mg/dL and/or an untreated total cholesterol level > 250 mg/dL.

iii. Patient has a treated low-density lipoprotein cholesterol (LDL-C) level ≥ 300 mg/dL AND meets one of the following (a or b); AND

Note: Treated refer to after therapy with at least one antihyperlipidemic agent. Some examples of antihyperlipidemic agents include statins (e.g., atorvastatin, rosuvastatin, lovastatin, simvastatin, pravastatin), ezetimibe, a PCSK9 inhibitor (e.g., Repatha® [evolocumab injection for subcutaneous use]), or Juxtapid® (lomitapide capsules).

a) Patient had clinical manifestations of homozygous familial hypercholesterolemia (HoFH) before the age of 10 years; OR

Note: Examples of clinical manifestations of HoFH are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma.

b) Both parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia (HeFH); AND

Note: An example of HeFH in both parents would be if both had an untreated LDL-C ≥ 190 mg/dL and/or an untreated total cholesterol > 250 mg/dL.

45. Patient meets one of the following criteria (i or ii):

i. Patient meets one of the following criteria (a, b, and c):
- **a)** Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin tablets ≥ 20 mg daily [as a single-entity or as a combination product]); AND
- **b)** Patient has tried one high-intensity statin along with ezetimibe (as a single entity or as a combination product) for ≥ 8 continuous weeks; AND
- **c)** The low-density lipoprotein cholesterol (LDL-C) level after this treatment regimen remains ≥ 70 mg/dL; OR

ii. Patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):
- **a)** Patient experienced statin-related rhabdomyolysis; OR
  Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]); OR
- **b)** Patient meets all of the following criteria [(1), (2), and (3)]:
  - **(1)** Patient experienced skeletal-related muscle symptoms; AND
    Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).
  - **(2)** The skeletal-related muscle symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND
  - **(3)** When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND
    Note: Examples of skeletal-related muscle symptoms include myopathy and myalgia.

46. Patient meets one of the following (i or ii):

i. Patient meets both of the following (a and b):
- **a)** Patient has tried a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor for ≥ 8 continuous weeks; AND
  Note: Examples of PCSK9 inhibitors include Repatha® (evolocumab injection for subcutaneous use) and Praluent® (alirocumab injection for subcutaneous use).
- **b)** The low-density lipoprotein cholesterol (LDL-C) level after this PCSK9 inhibitor therapy remains ≥ 70 mg/dL; OR

ii. Patient is known to have two LDL-receptor negative alleles; AND

47. Medication is prescribed by or in consultation with a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Evkeeza is not recommended in the following situations:

30. Heterozygous Familial Hypercholesterolemia (HeFH). The safety and effectiveness of Evkeeza have not been established in patients with hypercholesterolemia who do not have HoFH, including those with HeFH.[1]

31. Hyperlipidemia. Although data are available, the prescribing information for Evkeeza states that the safety and efficacy of Evkeeza have not been established in patients with other forms of hypercholesterolemia.[1,3]
Note: This is not associated with homozygous familial hypercholesterolemia and is referred to as combined hyperlipidemia, hypercholesterolemia (pure, primary), dyslipidemia, or increased/elevated low-density lipoprotein cholesterol (LDL-C) levels.

32. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	02/17/2021
Update	**Homozygous Familial Hypercholesterolemia:** The diagnostic criteria for HoFH were revised. To the criteria which stated that the patient has clinical manifestation of HoFH, the qualifier of "before the age of 10 years" was added. Also, this criterion is no longer an independent diagnostic but is now one of two criteria that must be met under the LDL-C threshold requirements (i.e., that the patient has an untreated LDL-C level > 500 mg/dL or a treated LDL-C ≥ 300 mg/dL). An additional criterion added to the two LDL-C threshold requirements is that the parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with HeFH with examples of these values provided. If the diagnostic pathway is sought through LDL-C thresholds, one of these two criteria must be met (i.e., clinical manifestations or parents of the patient have LDL-C or total cholesterol levels consistent with HeFH).	02/24/2021

HoFH – Homozygous familial hypercholeteorlemia; LDL-C – Low-density lipoprotein cholesterol; HeFH – Heterozygous familial hypercholesterolemia.

PRIOR AUTHORIZATION POLICY

POLICY: Homozygous Familial Hypercholesterolemia Juxtapid Prior Authorization Policy

- Juxtapid® (lomitapide capsules – Aegerion Pharmaceuticals)

REVIEW DATE: 10/14/2020

OVERVIEW

Juxtapid, a microsomal triglyceride transfer protein inhibitor, is indicated as an adjunct to a low fat diet and other lipid modifying therapies, including low-density lipoprotein (LDL) apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (total-C), apolipoprotein B (apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).[1] Limitations of use include that the safety and efficacy of Juxtapid have not been established in patients with hypercholesterolemia who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH).[1] Also, the effect of Juxtapid on cardiovascular (CV) morbidity and mortality have not been determined.

Repatha® (evolocumab injection for subcutaneous [SC] use), a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor, is indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with HoFH who require additional LDL-C lowering.[2] It is notable that patients known to have two LDL-receptor negative alleles (little or no residual function) did not respond

to Repatha. Repatha is well-tolerated and is not associated with hepatotoxicity.[2] Simvastatin, atorvastatin, and rosuvastatin are statins that are indicated for the management of patients with HoFH.[3-5] Ezetimibe is also indicated for use in combination with atorvastatin or simvastatin in patients with HoFH.[6] Ezetimibe/simvastatin tablets are indicated for use in HoFH.[7]

Disease Overview

Familial hypercholesterolemias encompass a group of genetic defects that cause severe elevations in LDL-C levels, as well as other lipid parameters.[8] The condition occurs in approximately 1 in 300 to 500 patients and is present in childhood. There are approximately 1 in one million people with HoFH that have extreme hypercholesterolemia with rapidly advancing atherosclerosis if untreated. Currently known causes of familial hypercholesterolemia include mutations in low-density lipoprotein receptor (LDLR), apolipoprotein B (apo B), or proprotein convertase subtilisin kexin type 9 (PCSK9) genes. Over 1,600 known mutations of the LDLR gene have been documented to cause familial hypercholesterolemia and account for about 85% to 90% of familial hypercholesterolemia cases. Patients with familial hypercholesteromia may have physical findings such as tendon xanthomas, which may occur at a young age. Individuals with familial hypercholesterolemia are at very high risk of coronary heart disease (CHD) at a premature age. Aggressive lipid modifying therapy is recommended to achieve LDL-C reductions of at least 50%. Both children and adults with LDL-C levels ≥ 190 mg/dL following lifestyle modifications will require medication therapy. Statins are the initial treatment for familial hypercholesteromia. Higher risk patients may require intensification of drug therapy to achieve the more aggressive treatment goals. Intensification of medication therapy should be considered if LDL-C remains ≥ 160 mg/dL or if an initial 50% reduction in LDL-C is not achieved. Other non-statin therapies that can be considered include ezetimibe, Repatha, a bile acid sequestrant (colesevelam tablets or oral suspension), or niacin. Most patients that cannot take a statin will require combination medication therapy. LDL apheresis is recommended in certain circumstances. Patients with HoFH should be managed by a lipid specialist.

Guidelines

In 2014, the European Atherosclerosis Society published recommendations regarding HoFH.[9] It notes that HoFH is a rare and life-threatening condition characterized by plasma cholesterol levels > 500 mg/dL, extensive xanthomas, and premature clinical atherosclerotic cardiovascular disease (ASCVD). If untreated, patients with extremely elevated LDL-C levels may develop atherosclerosis prior to the second decade of life. The frequency of HoFH is estimated at 1 in one million patients. The diagnosis of HoFH can be done by genetic or clinical criteria. Table 1 notes some criteria used by clinicians.

Table 1. Criteria for the Diagnosis of HoFH.[9]

- Genetic confirmation of two mutant alleles at the LDLR, Apo B, PCSK9 or LDLRAP1 gene locus; OR
- An untreated LDL-C > 500 mg/dL* or treated LDL-C > 300 mg/dL* together with either 1) cutaneous or tendon xanthoma before the age of 10 years or 2) untreated elevated LDL-C levels consistent with heterozygous FH in both parents.

HoFH – Homozygous familial hypercholesterolemia; LDLR – Low-density lipoprotein receptor; Apo B – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9; LDLRAP1 – Low-density lipoprotein receptor adaptor protein 1; LDL-C – Low-density lipoprotein cholesterol; * These cited LDL-C levels are only indicative and lower levels, especially in children or in untreated patients do not exclude HoFH; FH – Familial hypercholesterolemia.

The Consensus panel strongly recommends that lipid modifying therapy be initiated as early as possible based on evidence that treatment can delay the onset of clinically evident ASCVD.[9] LDL-C targets in HoFH are < 100 mg/dL in adults [< 135 mg/dL in children] or < 70 mg/dL in adults with clinical ASCVD. Statins have been the prominent treatment in HoFH, even among individuals who are receptor negative. Ezetimibe also provides further reduction. Combination therapy may also include other agents such as bile acid sequestrants, niacin and fibrates. LDL apheresis is also utilized and can decrease plasma LDL-C levels by 55% to 70% relative to pre-treatment levels. These guidelines were published before approval of Repatha which is indicated for use in HoFH.

Safety

Juxtapid has a Boxed Warnings regarding the risk of hepatotoxicity.[1] Juxtapid may cause elevations in liver transaminases. Also, Juxtapid increases hepatic fat (hepatic steatosis) with or without concomitant increases in transaminases. Due to the risk of hepatotoxicity, Juxtapid is available only through a Risk Mitigation and Strategy (REMS) Program. Juxtapid is a Pregnancy Category X medication and may cause fetal harm when given to a pregnant woman based on findings suggesting teratogenicity in animals. Females of reproductive potential should obtain a negative pregnancy test before Juxtapid initiation and should utilize effective contraception during Juxtapid use. Juxtapid is associated with gastrointestinal (GI) adverse events (AEs), which occurred in 93% of patients (n = 27/29). GI AEs included diarrhea (79%), nausea (65%), dyspepsia (38%), vomiting (34%), and abdominal pain (34%). Postmarketing reports regarding severe diarrhea have been associated with use of Juxtapid which have involved hospitalization of patients due to diarrhea-related complications such as volume depletion.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Juxtapid. All approvals are provided for the duration noted below. Because of the specialized skills required for managing patients with HoFH, approval requires Juxtapid to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: None required.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Juxtapid is recommended in those who meet the following criteria:

FDA-Approved Indication

2. Homozygous Familial Hypercholesterolemia (HoFH). Approve Juxtapid for 1 year if the patient meets the following criteria (A, B, C, D, and E):

48. Patient is aged ≥ 18 years; AND

49. Patient meets one of the following (i, ii, iii or iv):

- **i.** Patient has had genetic confirmation of two mutant alleles at the low-density lipoprotein receptor (LDLR), apolipoprotein B (apo B), proprotein convertase subtilisin kexin type 9 (PCSK9) or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene locus; OR
- **ii.** Patient has an untreated low-density lipoprotein cholesterol (LDL-C) level > 500 mg/dL (prior to treatment with antihyperlipidemic agents); OR
- **iii.** Patient has a treated LDL-C level ≥ 300 mg/dL (after treatment with antihyperlipidemic agents but prior to agents such as Repatha® [evolocumab injection for subcutaneous {SC} use]); OR
- **iv.** Patient has clinical manifestations of HoFH; AND

  Note: Examples of clinical manifestations of HoFH are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma.

50. Patient meets one of the following (i or ii):

- **i.** Patient meets both of the following (a and b):
  - **a)** Patient has tried Repatha (evolocumab injection for SC use); AND
  - **b)** Patient has experienced inadequate efficacy or significant intolerance according to the prescriber; OR
- **ii.** Patient is known to have two LDL-receptor negative alleles; AND

51. Patient meets one of the following criteria (i or ii):

- **i.** Patient meets both of the following criteria (a and b):

d) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin tablets ≥ 20 mg daily [as a single-entity or as a combination product])* for ≥ 8 continuous weeks; AND

e) The low-density lipoprotein cholesterol (LDL-C) level after this treatment regimen remains ≥ 70 mg/dL; OR

ii. Patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):

a) Patient experienced statin-related rhabdomyolysis; OR

Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase (CK) levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]); OR

b) Patient meets all of the following criteria [(1), (2), and (3)]:

(1) Patient experienced skeletal-related muscle symptoms; AND

Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

(2) The skeletal-related muscle symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND

(3) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms (e.g., myopathy, myalgia) resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND

52. Medication is prescribed by or in consultation with a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Juxtapid is not recommended in the following situations:

33. Concurrent use of Juxtapid with Praluent® (alirocumab for SC injection) or Repatha (evolocumab injection for SC use). Repatha, specifically indicated in HoFH, and Praluent are PCSK9 inhibitors and have not been adequately studied concomitantly with Juxtapid therapy.

34. Use of Juxtapid in Patients with Heterozygous Familial Hypercholesterolemia (HeFH). The safety and effectiveness of Juxtapid have not been established in patients with hypercholesterolemia who do not have HoFH, including those with HeFH.[1]

35. Use of Juxtapid in Patients with Other Forms of Hyperlipidemia (e.g., primary hyperlipidemia, mixed dyslipidemia). The safety and efficacy of Juxtapid have not been established in patients with hypercholesterolemia who do not have HoFH.[1]

36. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Kynamro no longer available. Therefore, Kynamro was removed from the listing of examples among the diagnostic criteria for HoFH in reference to the criterion that asks if the treated LDL-C level is ≥ 300 mg/dL (after treatment with antihyperlipidemic agents but prior to agents such as Repatha or Kynamro. Additionally, Kynamro was removed from the listing of medications in which Juxtapid cannot be used with concomitantly.	10/10/2018.
Annual Revision	No criteria changes.	10/09/2019
Annual Revision	**Homozygous Familial Hypercholesterolemia:** For the indication, the citation of "initial and continuing therapy" was removed. Examples of clinical manifestations of homozygous familial hypercholesterolemia were removed from the criteria and placed in a note. For the criteria which requires that the patient try Repatha, the wording that stated "the patient had an inadequate response according to the prescribing physician" was changed to the "patient experienced inadequate efficacy or significant intolerance according to the prescriber." For the criteria that requires that the patient try a statin, it was clarified that the requirement of the low-density lipoprotein cholesterol level remains ≥ 70 mg/dL was associated with "after this treatment regimen". Regarding the definition of rhabdomyolysis, the word "usually" was removed from the explanation associated with markedly elevated creatine kinase levels. Examples of skeletal-related muscle symptoms were moved from the criteria to a Note.	10/14/2020

PRIOR AUTHORIZATION POLICY

POLICY: Human Immunodeficiency Virus – Cabenuva Prior Authorization Policy

- Cabenuva® (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension, co-packaged – ViiV/GlaxoSmithKline)

REVIEW DATE: 02/03/2021

OVERVIEW

Cabenuva, a two-drug co-packaged product of cabotegravir, a human immunodeficiency virus type-1 (HIV-1) integrase strand-transfer inhibitor, and rilpivirine, an HIV-1 non-nucleoside reverse transcriptase inhibitor, is **indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace their current antiretroviral (ARV) regimen in those who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable ARV regimen with no history of treatment failure and with no known or suspected resistance to cabotegravir or rilpivirine**.[1]

Cabenuva must be administered by a healthcare professional. Prior to starting Cabenuva, healthcare professionals should carefully select patients who agree to the required monthly injection dosing schedule and counsel patients about the importance of adherence to scheduled dosing visits to help maintain viral suppression and reduce the risk of viral rebound and potential development of resistance with missed doses.[1]

Oral lead-in with Vocabria® (cabotegravir tablets) + Edurant® (rilpivirine tablets) should be used for approximately 1 month (at least 28 days) prior to the initiation of Cabenuva to assess the tolerability of cabotegravir and rilpivirine. On the last day of oral lead-in, the first dose of Cabenuva (600 mg/900 mg) is administered; monthly doses of Cabenuva (400 mg/600 mg) are administered starting at Month 3.

Table 1. Recommended Oral Lead-In and IM Injection Dosing Schedule in Adults.[1]

Vocabria + Edurant Lead-In (at Least 28 Days)	Cabenuva Initiation Injections (One-Time Dosing)	Cabenuva Continuation Injections (Once-Monthly Dosing)
Month 1	At Month 2 (On the Last Day of Oral Lead-In Dosing)	Month 3 Onwards
Vocabria (30 mg) QD with a meal	cabotegravir 600 mg (3 mL)	cabotegravir 400 mg (2 mL)
Edurant (25 mg) QD with a meal	rilpivirine 900 mg (3 mL)	rilpivirine 600 mg (2 mL)

IM – Intramuscular.

If monthly Cabenuva doses are missed or delayed by > 7 days and oral therapy has not been taken in the interim, clinically reassess the patient to determine if resumption of Cabenuva remains appropriate. If Cabenuva will be continued, see Table 2 for dosing recommendations.

Table 2. Cabenuva Dosing Recommendation after Missed Injections*.[1]

Time Since Last Dose of Cabenuva	Recommendation
≤ 2 months	Resume with 400 mg (2 mL) cabotegravir and 600 mg (2 mL) rilpivirine IM monthly injections as soon as possible.
> 2 months	Re-initiate the patient with 600 mg (3 mL) cabotegravir and 900 mg (3 mL) rilpivirine IM injections then continue to follow the 400 mg (2 mL) cabotegravir and 600 mg (2 mL) rilpivirine IM monthly injection dosing schedule.

*Refer to oral dosing recommendations if a patient plans to miss a scheduled injection visit; IM – Intramuscular.

Clinical Efficacy

The use of Vocabria + Edurant as an oral lead-in and Cabenuva once monthly for maintenance therapy in adults with HIV-1 was evaluated in two published, Phase III, randomized, multicenter, active-controlled, parallel-arm, open-label, non-inferiority pivotal trials (FLAIR and ATLAS).[3,4] In FLAIR, patients were naïve to antiretroviral therapy and started on Triumeq® (abacavir/dolutegravir/lamivudine tablets) for 20 weeks then continued on Triumeq or were switched to the long-acting regimen of Vocabria/Cabenuva in accordance with the FDA-approved dosing regimen.[3] In ATLAS, patients who were virally suppressed on an oral antiretroviral regimen (excluding Triumeq) continued on their antiretroviral regimen or were switched to the long-acting regimen of Vocabria/Cabenuva in accordance with the FDA-approved dosing regimen.[4] In FLAIR (n = 566), at Week 48, the long-acting regimen was non-inferior to Triumeq; 2.1% and 2.5% of patients, respectively, did not maintain viral suppression (adjusted difference -0.4%; 95% confidence interval [CI]: -2.8, 2.1).[3] In ATLAS (n = 618), at Week 48, the long-acting regimen was non-inferior to patients existing oral antiretrovirals: 1.6% and 1.0% of patients, respectively, did not maintain viral suppression (adjusted difference 0.6%; 95% CI: -1.2, 2.5).[4]

Guidelines

Cabenuva is addressed as an unapproved product in the International Antiviral Society-USA (IAS-USA) Panel Recommendations for Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults (2020); Cabenuva and Vocabria have not been addressed in the Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV (last updated December 18, 2019).[4,5]

According to the IAS-USA, in the setting of viral suppression, switching from a three-drug regimen to a two-drug regimen is an appropriate strategy to manage toxic side effects, intolerance, adherence, or patient preference provided

that both agents are fully active.[4] Recommended regimens include: dolutegravir/lamivudine (available as Dovato® [dolutegravir/lamivudine tablets] or Tivicay® [dolutegravir tablets] + lamivudine [Epivir®, generics]), dolutegravir/rilpivirine (available as Juluca® [dolutegravir/rilpivirine tablets] or Tivicay + Edurant), a boosted protease inhibitor (lopinavir, atazanavir [Reyataz®, generics], or darunavir [Prezista®, generics]) + lamivudine, or a long-acting injectable two-drug regimen of Cabenuva pending approval by regulatory bodies and availability. The DHHS guidelines provide identical examples of successful strategies for switching from three-drug to two-drug regimens in individuals with suppressed HIV (with the noted absence of Cabenuva likely due to the timing of the last update).[5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cabenuva. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cabenuva as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Cabenuva to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cabenuva is recommended in those who meet the following criteria:

FDA-Approved Indications

71. Human Immunodeficiency Virus (HIV). Approve for the duration below if the patient meets ONE of the following conditions (A or B):

- **A)** Initial Therapy: Approve for 1 year if the patient meets all of the following (i, ii, iii, iv, and v):
  - **i.** Patient is ≥ 18 years of age; AND
  - **ii.** Patient has HIV type-1 (HIV-1) infection; AND
  - **iii.** Patient has HIV-1 RNA < 50 copies/mL (viral suppression); AND
  - **iv.** Patient has completed, or will complete, and tolerated 1 month of therapy with Vocabria (cabotegravir tablets) + Edurant (rilpivirine tablets), according to the prescriber; AND
  - **v.** The medication is prescribed by or in consultation with a physician who specializes in the treatment of HIV infection.
- **B)** Patient is Currently Receiving Cabenuva: Approve for 1 year if the patient meets all of the following (i and ii):
  - **i.** Patient has HIV type-1 (HIV-1) infection; AND
  - **ii.** Patient has HIV-1 RNA < 50 copies/mL (viral suppression).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cabenuva is not recommended in the following situations:

79. Pre-exposure Prophylaxis (PrEP). Cabenuva is not indicated for the prevention of human immunodeficiency virus (HIV) in patients who are uninfected, but at risk of acquisition of HIV. Data from two unpublished trials have demonstrated the superiority of cabotegravir extended-release injectable suspension to Truvada® (tenofovir disoproxil fumarate/emtricitabine tablets, generics) for PrEP in cisgender men and transgender men who have sex with men as well as in cisgender women.[5] IAS-USA guidelines recommend cabotegravir extended-release injectable suspension for PrEP in cisgender men and transgender women who have sex with men; every 8 week maintenance dosing is recommended and oral lead-in with Vocabria is optional.[4] The other recommended regimens for PrEP

are daily Truvada (all at-risk populations) or Descovy® (tenofovir alafenamide/emtricitabine tablets) [MSM with/at risk for kidney dysfunction, osteopenia, or osteoporosis]. Truvada and Descovy are FDA-approved for PrEP; neither Vocabria nor Cabenuva are FDA-approved for PrEP.

80. Human Immunodeficiency Virus, Antiretroviral Treatment-Naïve Patients. Cabenuva is indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace their current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to cabotegravir or rilpivirine.[1] In two pivotal trials, patients were either previously treated for 4 months (20 weeks) with Triumeq® (abacavir/dolutegravir/lamivudine tablets) or were on a stable antiretroviral regimen for ≥ 6 months.[2,3]

81. Co-administration with Antiretrovirals for Human Immunodeficiency Virus. Because Cabenuva is a complete regimen, co-administration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended.[1]

82. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	02/03/2021

PRIOR AUTHORIZATION POLICY

POLICY: Human Immunodeficiency Virus – Rukobia Prior Authorization Policy

- Rukobia™ (fostemsavir extended-release tablets – ViiV)

REVIEW DATE: 07/22/2020

OVERVIEW

Rukobia, a human immunodeficiency virus type-1 (HIV-1) gp120-directed attachment inhibitor, in combination with other antiretroviral(s) [ARVs], is indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current ARV regimen due to resistance, intolerance, or safety considerations.[1]

Disease Overview

Heavily treatment-experienced adults account for approximately 6% of adults living with HIV who are on ARV treatment.[2] These patients have few, if any, treatment options left due to resistance, tolerability, and/or safety

considerations. Heavily treatment-experienced adults are at greater risk of progression to acquired immunodeficiency syndrome (AIDS) and death than non-heavily treatment-experienced adults.

Clinical Efficacy

The efficacy of Rukobia was established in one ongoing, Phase III, multicenter, 96-week pivotal study in Heavily treatment-experienced adults with HIV-1 infection failing their current ARV regimen (BRIGHTE; n = 371).[3,6] Eligible patients were ≥ 18 years of age and had failure of their current ARV regimen (baseline HIV-1 RNA ≥ 400 copies/mL), with no viable ARV combination therapy available because of exhaustion of a least four of six ARV classes (nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, integrase inhibitors, protease inhibitors, CCR5 antagonists, and entry inhibitors). Exhaustion was defined as the elimination of all ARVs within a given class as a fully active option to pair with Rukobia because of resistance, previous adverse events (AEs), or unwillingness to use Fuzeon® (enfuviritide injection). There were 15 patients who received Trogarzo® (ibalizumab-uiyk injection) in combination with Rukobia.

Guidelines

Treatment with Rukobia is not addressed in guidelines. According to the Department of Health and Human Services Guidelines (December 18, 2019) for the use of antiviral agents in adults and adolescents with HIV infection, treatment-experienced patients with ongoing detectable viremia who lack sufficient treatment options to construct a fully suppressive regimen may be candidates for Trogarzo.[4] Patients who continue to have detectable viremia and who lack sufficient treatment options to construct a fully suppressive regimen may also be candidates for research studies or expanded access programs, or they may qualify for single-patient access to an investigational new drug as specified in FDA regulations. Guidelines note that Rukobia as an agent in late-stage clinical studies. The International Antiviral Society-USA recommendations for the treatment and prevention of HIV in adults (2018) note that Trogarzo may be useful as a fully active agent for patients with multiclass-resistant virus.[5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Rukobia. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Rukobia as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Rukobia to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rukobia is recommended in those who meet the following criteria:

FDA-Approved Indications

72. Human Immunodeficiency Virus (HIV) Infection. Approve for the duration noted if the patient meets ONE of the following (A or B):

- **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following conditions (i, ii, iii, iv, v, and vi):
  - **i.** The patient is ≥ 18 years of age; AND
  - **ii.** The patient has human immunodeficiency virus type-1 (HIV-1) infection; AND
  - **iii.** According to the prescriber, the patient is failing a current antiretroviral regimen for human immunodeficiency virus (HIV); AND
  - **iv.** According to the prescriber, the patient has exhausted at least FOUR of the following antiretroviral classes, defined as elimination of all antiretrovirals within a given class due to demonstrated or projected resistance to the agent(s) in that class OR due to significant intolerance:
    - **a)** Nucleoside reverse transcriptase inhibitor; OR

Note: Examples of nucleoside reverse transcriptase inhibitors include abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir disoproxil fumarate, tenofovir alafenamide, zidovudine.

b) Non-nucleoside reverse transcriptase inhibitor; OR
Note: Examples of non-nucleoside reverse transcriptase inhibitor include delaviridine, efavirenz, etravirine, nevirapine, nevirapine XR, rilpivirine.

c) Protease inhibitor; OR
Note: Examples of protease inhibitors include atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, tipranavir.

d) Fusion inhibitor; OR
Note: Examples of fusion inhibitors include Fuzeon (enfuviritide for injection).

e) Integrase strand transfer inhibitor; OR
Note: Examples of integrase strand transfer inhibitors include raltegravir, dolutegravir, elvitegravir.

f) CCR5-antagonist; AND
Note: Examples of CCR5 antagonists include Selzentry® (maraviroc tablets).

v. The requested agent will be taken in combination with an optimized antiviral background regimen including one or more other antiretroviral agents; AND

vi. The requested agent is prescribed by or in consultation with a physician who specializes in the treatment of HIV infection.

B) Patient is Currently Receiving Rukobia. Approve for 1 year if the patient meets ALL of the following conditions (i, ii, and iii):

i. Patient has human immunodeficiency virus type-1 (HIV-1) infection; AND

ii. The requested agent will continue to be taken in combination with an optimized antiviral background regimen including one or more other antiretroviral agents; AND

iii. The patient has responded to a Rukobia-containing regimen, as determined by the prescriber.
Note: Examples of a response are HIV RNA < 40 cells/mm^3, HIV-1 RNA $\geq$ 0.5 $\log_{10}$ reduction from baseline in viral load.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rukobia is not recommended in the following situations:

83. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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51. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. Last Updated: December 18, 2019. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed July 6, 2020.
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6. Lataillade M, Lalezari J, Molina J-M, et al. Week 96 safety and efficacy of the novel HIV-1 attachment inhibitor prodrug fostemsavir in heavily treatment-experienced participants infected with multi-drug resistant HIV-1 (BRIGHTE study) [abstract MOAB0102]. Presented at: 10th International AIDS Society Conference on HIV Science; Mexico City, Mexico; July 21-24, 2019.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/22/2020
DEU Revision	Removal of criterion note referencing CD4 T-cell count	08/03/2020

PRIOR AUTHORIZATION POLICY

POLICY: Human Immunodeficiency Virus – Trogarzo™ (ibalizumab-uiyk injection for intravenous use – Theratechnologies)

TAC APPROVAL DATE: 04/08/2020

OVERVIEW

Trogarzo is a long-acting humanized immunoglobulin G4 monoclonal antibody indicated in combination with other antiretroviral(s) [ARV{s}] for the treatment of human immunodeficiency virus type-1 (HIV-1) infection in heavily treatment-experienced adults with multidrug resistant (MDR) HIV-1 infection failing their current ARV regimen.[1] It is a chronic therapy administered by a trained healthcare professional intravenously (IV), after diluting the appropriate number of vials in 250 mL of 0.9% Sodium Chloride Injection, USP. Patients should receive a single loading dose of 2,000 mg followed by a maintenance dose of 800 mg once every 2 weeks (Q2W). Trogarzo is available in a single-dose, 2 mL vial containing 150 mg/mL of ibalizumab-uiyk. Each vial delivers approximately 1.33 mL containing 200 mg of ibalizumab-uiyk.

Disease Overview

Multiclass or three-class drug resistant HIV-1 infection is usually defined as the presence of phenotypic or genotypic resistance to resistance to at least one drug in each of the following three classes: the nucleoside reverse transcriptase inhibitors (NRTIs)-, non-nucleoside reverse transcriptase inhibitors (NNRTIs)-, and protease inhibitors (PIs)-classes.[2] Trogarzo blocks HIV-1 from infecting CD4+ T cells by binding to domain 2 of CD4.[1] This interferes with post-attachment steps required for the entry of HIV-1 virus particles into host cells and prevents the viral transmission that occurs via cell-cell fusion. The binding specificity to domain 2 of CD4 allows Trogarzo to block viral entry into host cells without causing immunosuppression. There is no antagonism with other ARVs.

In the pivotal trial for Trogarzo, all patients had documented resistance to at least one ARV from the NRTI, NNRTI, and PI classes. The Table below provides examples of drugs from each class. NOTE: This is not all inclusive.

Table 1. Examples of HIV ARVs by Class.

Drug Class	Examples
NRTIs	Ziagen® (abacavir), Videx EC® (didanosine delayed-release), Videx® Pediatric (didanosine), Emtriva® (emtricitabine), Epivir®, (lamivudine), Zerit®, (stavudine), Viread®, (tenofovir disoproxil fumarate), Retrovir® (zidovudine), Combivir® (lamivudine/zidovudine), Epzicom® (abacavir/lamivudine), Trizivir® (abacavir/lamivudine/zidovudine), Truvada® (emtricitabine/tenofovir disoproxil fumarate), Descovy® (emtricitabine/tenofovir alafenamide)
NNRTIs	Rescriptor® (delavirdine), Sustiva® (efavirenz), Intelence® (etravirine), Viramune® (nevirapine), Viramune® XR™ (nevirapine XR), Edurant® (rilpivirine)
PIs	Reyataz® (atazanavir), Prezista® (darunavir), Lexiva® (fosamprenavir), Crixivan® (indinavir), Viracept® (nelfinavir), Norvir® (ritonavir), Invirase® (saquinavir), Aptivus® (tipranavir), Kaletra® (lopinavir/ritonavir), Prezcobix® (darunavir/cobicistat), and Evotaz® (atazanavir/cobicistat)

Table 1 (continued). Examples of HIV ARVs by Class.

Drug Class	Examples
INSTIs	Isentress® (raltegravir), Isentress® HD (raltegravir), Tivicay® (dolutegravir), and Vitekta® (elvitegravir)
Fusion Inhibitor	Fuzeon® (enfuviritide)
CCR5-Antagonist	Selzentry® (maraviroc tablets)
Combination Products	Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide tablets), Dutrebis™ (lamivudine/raltegravir potassium), Complera® (emtricitabine/rilpivirine/tenofovir disoproxil fumarate), Odefsey® (emtricitabine/rilpivirine/tenofovir alafenamide), Atripla® (efavirenz/ emtricitabine/tenofovir disoproxil fumarate), Stribild® (cobicistat/elvitegravir/emtricitabine/tenofovir disoproxil fumarate), Triumeq® (abacavir/dolutegravir/lamivudine), and Genvoya® (cobicistat/elvitegravir/emtricitabine/tenofovir alafenamide), Symtuza® (darunavir/cobicistat/emtricitabine/tenofovir alafenamide)

HIV – Human immunodeficiency virus; ARVs – Antiretrovirals; NRTIs – Nucleoside reverse transcriptase inhibitors; NNRTIs – Non-nucleoside reverse transcriptase inhibitors; PIs – Protease inhibitor; INSTIs – Integrase strand-transfer inhibitor.

Guidelines

The Department of Health and Human Services (DHHS) guidelines for the treatment of adults and adolescents with HIV-1 recognize the difficulty in treating patients with extensive resistance.[3] Managing patients with extensive resistance is complex and usually requires consultation with an HIV expert. Patients with ongoing detectable viremia who lack sufficient treatment options to construct a fully suppressive regimen may be candidates for Trogarzo.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Trogarzo. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the of the specialized skills required for evaluation and diagnosis of patients treated with Trogarzo as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Trogarzo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Trogarzo is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Human Immunodeficiency Virus (HIV) Infection.** Approve for the duration outlined below if the patients meets ONE of the following conditions (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following conditions (i, ii, iii, iv, v, and vi):
     - **iv.** The patient is ≥ 18 years of age; AND
     - **v.** The patient has an HIV type 1 infection; AND
     - **vi.** According to the prescribing physician, the patient is failing a current antiretroviral regimen for HIV; AND
     - **vii.** The patient has multiple antiretroviral drug resistance as demonstrated by resistance to at least one antiretroviral from at least THREE of the following antiviral classes:
       - **a)** nucleoside reverse transcriptase inhibitor (NRTI) [e.g., abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir disoproxil fumarate, tenofovir alafenamide, zidovudine]; OR
       - **b)** non-nucleoside reverse transcriptase inhibitor (NNRTI) [e.g., delaviridine, efavirenz, etravirine, nevirapine, nevirapine XR, rilpivirine]; OR
       - **c)** protease inhibitor (PI) [e.g., atazanavir, darunavir), fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, tipranavir]; OR
       - **d)** fusion inhibitor [e.g., Fuzeon® (enfuviritide for injection)]; OR
       - **e)** integrase strand transfer inhibitor (INSTI) [e.g., raltegravir, raltegravir, dolutegravir, and elvitegravir]; OR

f) CCR5-antagonist [e.g., Selzentry® (maraviroc tablets)]; AND

viii. The requested agent will be taken in combination with an optimized antiviral background regimen including one or more other antiretroviral agents; AND

ix. The requested agent is prescribed by or in consultation with a physician who specializes in the treatment of human immunodeficiency virus (HIV) infection.

B) Patients Currently Receiving Trogarzo. Approve for 1 year if the patient meets ALL of the following conditions (i, ii, and iii):

i. The patient has an HIV type 1 infection; AND

ii. The requested agent will continue to be taken in combination with an optimized antiviral background regimen including one or more other antiretroviral agents; AND

iii. The patient has responded (e.g., HIV-1 RNA $\geq$ 0.5 $\log_{10}$ reduction from baseline in viral load) to a Trogarzo-containing regimen, as determined by the prescribing physician.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Trogarzo has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

84. Human Immunodeficiency Virus (HIV), Type 2. Trogarzo has only been evaluated in HIV-1 infection. The Department of Health and Human Services (DHHS) guidelines for the treatment of adults and adolescents with HIV-1 state that there are no data on the activity of Trogarzo against HIV-2.[3]

85. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Trogarzo™ injection [prescribing information]. Montreal, Quebec, Canada: Theratechnologies, Inc; May 2018.
2. Imaz, A, Falco V, Ribera E, et al. Antiretroviral salvage therapy for multiclass drug-resistant HIV-1-infected patients: From clinical trials to daily clinical practice. AIDS. 2011;13:180-193.
3. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed March 30, 2020. Updated December 18, 2019.

OTHER REFERENCES UTILIZED

- Emu B, Fessel J, Schrader S, et al. Phase III study of ibalizumab for multidrug-resistant HIV-1. *N Engl J Med.* 2018;379:645-654.
- Emu B, Lalezari J, Kumar P, et al. Ibalizumab: 96-week data and efficacy in patients resistant to common antiretrovirals [poster]. Presented at: the Conference on Retroviruses and Opportunistic Infections; Seattle, WA; March 4-7. 2019.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
New Policy	--	04/03/2019
Annual Revision	No criteria changes	04/08/2020

* For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx; TAC – Therapeutic Assessment Committee.

PRIOR AUTHORIZATION POLICY

POLICY: Human Immunodeficiency Virus – Vocabria Prior Authorization Policy

- Vocabria® (cabotegravir tablets – ViiV/GlaxoSmithKline)

REVIEW DATE: 02/03/2021

OVERVIEW

Vocabria, a human immunodeficiency virus type-1 (HIV-1) integrase strand-transfer inhibitor, is indicated **in combination with Edurant® (rilpivirine tablets) for the short-term treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine, for use as**:[1]

- **Oral lead-in** to assess the tolerability of cabotegravir prior to administration of Cabenuva® (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension, co-packaged).
- **Oral therapy for patients who will miss planned injection dosing with Cabenuva**.

For oral lead-in, the recommended dose is Vocabria 30 mg QD + Edurant 25 mg QD at approximately the same time each day with a meal for approximately 1 month (28 days).[1] The last oral dose should be taken on the same day monthly injections with Cabenuva injections are started.

If a patient plans to miss scheduled monthly injections of Cabenuva by > 7 days, daily oral therapy is taken to replace up to two consecutive monthly injection visits.[1] The first dose of Vocabria 30 mg + Edurant 25 mg should be taken approximately 1 month after the last maintenance injection dose of Cabenuva and continued until the day injection dosing is restarted.[1,6]

Clinical Efficacy

The use of Vocabria + Edurant as an oral lead-in and Cabenuva once monthly for maintenance therapy in adults with HIV-1 was evaluated in two published, Phase III, randomized, multicenter, active-controlled, parallel-arm, open-label, non-inferiority pivotal trials (FLAIR and ATLAS).[3,4] In FLAIR, patients were naïve to antiretroviral therapy and started on Triumeq® (abacavir/dolutegravir/lamivudine tablets) for 20 weeks then continued on Triumeq or were switched to the long-acting regimen of Vocabria/Cabenuva in accordance with the FDA-approved dosing regimen.[3] In ATLAS, patients who were virally suppressed on an oral antiretroviral regimen (excluding Triumeq) continued on their antiretroviral regimen or were switched to the long-acting regimen of Vocabria/Cabenuva in accordance with the FDA-approved dosing regimen.[4] In FLAIR (n = 566), at Week 48, the long-acting regimen was non-inferior to Triumeq; 2.1% and 2.5% of patients, respectively, did not maintain viral suppression (adjusted difference -0.4%; 95% confidence interval [CI]: -2.8, 2.1).[3] In ATLAS (n = 618), at Week 48, the long-acting regimen was non-inferior to patients existing oral antiretrovirals: 1.6% and 1.0% of patients, respectively, did not maintain viral suppression (adjusted difference 0.6%; 95% CI: -1.2, 2.5).[4]

Guidelines

Cabenuva is addressed as an unapproved product in the International Antiviral Society-USA (IAS-USA) Panel Recommendations for Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults (2020); Cabenuva and Vocabria have not been addressed in the Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV (last updated December 18, 2019).[4,5]

According to the IAS-USA, in the setting of viral suppression, switching from a three-drug regimen to a two-drug regimen is an appropriate strategy to manage toxic side effects, intolerance, adherence, or patient preference provided that both agents are fully active.[4] Recommended regimens include: dolutegravir/lamivudine (available as Dovato® [dolutegravir/lamivudine tablets] or Tivicay® [dolutegravir tablets] + lamivudine [Epivir®, generics]), dolutegravir/rilpivirine (available as Juluca® [dolutegravir/rilpivirine tablets] or Tivicay + Edurant), a boosted protease inhibitor (lopinavir, atazanavir [Reyataz®, generics], or darunavir [Prezista®, generics]) + lamivudine, or a long-acting injectable two-drug regimen of Cabenuva pending approval by regulatory bodies and availability. The DHHS guidelines provide identical examples of successful strategies for switching from three-drug to two-drug regimens in individuals with suppressed HIV (with the noted absence of Cabenuva likely due the timing of the last update).[5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vocabria. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vocabria as well as the monitoring required for adverse events and long-term efficacy, approval requires Vocabria to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vocabria is recommended in those who meet the following criteria:

FDA-Approved Indications

73. Human Immunodeficiency Virus (HIV), Oral Lead-In to Assess the Tolerability of cabotegravir.
Approve for 1 month if the patient meets the following criteria (A, B, C, D, E, F, and G):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has HIV type-1 (HIV-1) infection; AND
- **C)** Patient has HIV-1 RNA < 50 copies/mL (viral suppression); AND
- **D)** Patient is currently receiving antiretrovirals for the treatment of HIV-1 with a stable regimen (≥ 4 months); AND
- **E)** The medication will be prescribed in combination with Edurant (rilpivirine tablets); AND
- **F)** If tolerated, Cabenuva (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension, co-packaged) will be started upon completion of approximately 1 month of therapy with Vocabria + Edurant; AND
- **G)** The medication is prescribed by or in consultation with a physician who specializes in the treatment of HIV infection.

74. Human Immunodeficiency Virus (HIV), Oral Therapy for Planned Missed Doses of Cabenuva.
Approve for up to 2 months if the patient meets the following criteria (A, B, C, D, E, F, and G):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has HIV type 1 (HIV-1) infection; AND
- **C)** Patient has HIV-1 RNA < 50 copies/mL (viral suppression); AND
- **D)** Patient has received ≥ 1 maintenance dose of Cabenuva (400 mg/600 mg); AND
- **E)** Patient plans to miss up to two scheduled doses of Cabenuva by > 7 days, according to the prescriber; AND
- **F)** The medication will be prescribed in combination with Edurant (rilpivirine tablets); AND
- **G)** The medication is prescribed by or in consultation with a physician who specializes in the treatment of HIV infection.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vocabria is not recommended in the following situations:

86. Pre-exposure Prophylaxis (PrEP). Vocabria is not currently indicated for the prevention of human immunodeficiency virus (HIV) in patients who are uninfected, but at risk of acquisition of HIV. Data from two unpublished trials have demonstrated the superiority of cabotegravir extended-release injectable suspension to Truvada® (tenofovir disoproxil fumarate/emtricitabine tablets, generics) in cisgender men and transgender men who have sex with men as well as in cisgender women.[5] IAS-USA guidelines recommend cabotegravir extended-release injectable suspension in cisgender men and

transgender women who have sex with men; every 8 week maintenance dosing is recommended and oral lead-in with Vocabria is optional.[4] The other recommended regimens for PrEP are daily Truvada (all at-risk populations) or Descovy® (tenofovir alafenamide/emtricitabine tablets) [MSM with/at risk for kidney dysfunction, osteopenia, or osteoporosis]. Truvada and Descovy are FDA-approved for PrEP; neither Vocabria nor Cabenuva are FDA-approved for PrEP.

87. **Human Immunodeficiency Virus, Antiretroviral Treatment-Naïve Patients.** Vocabria is indicated in combination with Edurant (rilpivirine tablets) for the short-term treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine.[1] In two pivotal trials, patients were either previously treated for 4 months (20 weeks) with Triumeq® (abacavir/dolutegravir/lamivudine tablets) or were on a stable antiretroviral regimen for ≥ 6 months.[2,3]

88. **Duration of Use for > 2 Consecutive Months.** The recommended duration of Vocabria therapy is 1 month for oral lead-in.[1] Vocabria is also indicated as a daily regimen to replace up to two planned missed injections of Cabenuva (administered once monthly) for up to two consecutive months.

89. **Co-administration with Antiretrovirals for Human Immunodeficiency Virus other than Edurant.** Because Vocabria in combination with Edurant (rilpivirine tablets) is a complete regimen, co-administration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended.[1]

90. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

239. Vocabria® tablets [prescribing information]. Research Triangle Park, NJ: ViiV Healthcare/GlaxoSmithKline; January 2021.
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242. Saag MS, Gandhi RT, Hoy JF, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults. 2020 recommendations of the International Antiviral Society-USA Panel. *JAMA.* 2020;324(16):1651-1669.
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244. Personal communication. ViiV Healthcare. January 28, 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	02/03/2021

PRIOR AUTHORIZATION POLICY

POLICY: Hyaluronic Acid Derivatives Intraarticular Prior Authorization Policy

- Durolane® (sodium hyaluronate injection – Bioventus)
- Euflexxa® (sodium hyaluronate injection – Ferring Pharmaceuticals)
- Gel-One® (sodium hyaluronate injection – Seikagaku Corporation/Zimmer)
- Gelsyn-3™ (sodium hyaluronate injection – Bioventus)
- GenVisc® 850 (sodium hyaluronate injection – OrthogenRx)
- Hyalgan® (sodium hyaluronate injection – Fidia Pharma)
- Hymovis® (high molecular weight viscoelastic hyaluronan injection – Fidia Pharma)
- Monovisc™ (high molecular weight hyaluronan injection – DePuy Mitek/Johnson & Johnson)
- Orthovisc® (high molecular weight hyaluronan injection – DePuy Mitek/Johnson & Johnson)
- Supartz FX™ (sodium hyaluronate injection – Bioventus)
- Sodium hyaluronate 1% injection – Teva
- Synvisc® (hylan G-F 20 sodium hyaluronate injection – Genzyme)
- Synvisc-One® (hylan G-F 20 sodium hyaluronate injection – Genzyme)
- Triluron™ (sodium hyaluronate injection – Fidia Pharma)
- TriVisc™ (sodium hyaluronate injection – OrthogenRx)
- Visco-3™ (sodium hyaluronate injection –Bioventus)

REVIEW DATE: 08/26/2020

OVERVIEW

Hyaluronic acid derivatives are indicated for the treatment of pain related to knee osteoarthritis in patients who have failed to respond adequately to conservative nonpharmacologic therapy and to simple analgesics (e.g., acetaminophen).[1-16] The use of intraarticular injections are to restore the normal properties (viscosity and elasticity) of the synovial fluid. Gel-One, Hyalgan, Supartz FX, Synvisc/Synvisc-One, Triluron, and Visco-3 are derived from rooster or chicken combs. The remaining products are derived from non-avian sources and may be useful for patients with allergies to eggs or poultry products. GenVisc 850 has data to support similarity to Supartz FX.[9] All of the products given as a series of five injections (GenVisc 850,

Hyalgan, and Supartz FX) have a corresponding product that is equivalent to three injections (TriVisc, Triluron, and Visco-3, respectively). Although retreatment data are limited, all of these products have data concerning efficacy and/or safety of repeat courses. In many cases, at least 6 months was required or a minimum of 6 months had elapsed prior to injection of a repeat course.

Guidelines

Guidelines for the medical management of osteoarthritis of the hand, hip, and knee are available from the American College of Rheumatology (2019).[17] Multiple non-pharmacological modalities are recommended for knee osteoarthritis, including exercise, self-management programs, weight loss, Tai Chi, and use of assistive devices (i.e., bracing or a cane). Pharmacologic therapy for knee osteoarthritis consists of acetaminophen, oral and topical non-steroidal anti-inflammatory drugs (NSAIDs), tramadol, intraarticular corticosteroid injections, duloxetine, and topical capsaicin. There is limited evidence establishing a benefit of hyaluronic acid intraarticular injections, which contributes to the conditional recommendation against use in knee osteoarthritis. However, when other alternatives have been exhausted or have failed to provide satisfactory benefit, use of intraarticular hyaluronic acid injections may be viewed more favorably than offering no intervention. In the guidelines, no distinction is made between the available intraarticular hyaluronic acid products or between products with various molecular weights.

The Osteoarthritis Research Society International also has guidelines for knee osteoarthritis (2019).[19] These guidelines note that use of intraarticular hyaluronic acid injections are conditionally recommended for patients with knee osteoarthritis. The guidelines comment on the long-term treatment effect with intraarticular hyaluronic acid injections which is associated with symptom improvement beyond 12 weeks and a move favorable safety profile than intraarticular corticosteroid injections.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of hyaluronic acid derivatives indicated for knee osteoarthritis. Because of the specialized skills required for evaluation and diagnosis of patients treated with hyaluronic acid derivative intraarticular products as well as the specialized administration technique, these products are required to be administered by or under the supervision of a physician specializing in rheumatology, orthopedic surgery, or physical medicine and rehabilitation (physiatrist). All approvals are provided for one course of therapy per treated knee. Note that 1 month is a sufficient approval duration for one course of Durolane, Euflexxa, Gel-One, Gelsyn-3, Hymovis, Monovisc, sodium hyaluronate 1% injection, Synvisc, Synvisc-One, Triluron, TriVisc, and Visco-3; 5 weeks is a sufficient approval duration for one course of GenVisc 850, Orthovisc, Hyalgan, and Supartz FX. Previous therapy is required to be verified by a clinician in the Coverage Review Department when noted in the criteria as **[verification of therapies required].**

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of hyaluronic acid derivatives is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Osteoarthritis of the Knee.** Approve one course of therapy per treated knee if the patient meets ONE of the following conditions (A or B):
   - **A)** Initial Therapy. Approve an initial course if the patient meets ALL of the following conditions (i, ii, and iii):

i. Diagnosis of the knee to be treated is confirmed by radiologic evidence of knee osteoarthritis; AND
Note: Examples of radiographic evidence includes x-ray, magnetic resonance imaging (MRI), computed tomography (CT) scan, ultrasound.

ii. Patient has tried at least TWO of the following three modalities of therapy for osteoarthritis (a, b, c):

a) At least one course of physical therapy for knee osteoarthritis;

b) At least TWO of the following pharmacologic therapies [(1), (2), (3), (4)] **[verification of therapies required]**:

(1) Oral or topical nonsteroidal anti-inflammatory drug(s) [NSAID(s)];
Note: Examples of oral NSAIDs include naproxen, ibuprofen, celecoxib. Examples of topical NSAIDs include diclofenac solution or diclofenac gel. A trial of two or more NSAIDs (oral and/or topical) counts as one pharmacologic therapy.

(2) Acetaminophen;

(3) Tramadol (Ultram®/XR, generics);

(4) Duloxetine (Cymbalta®, generics);

c) At least TWO injections of intraarticular corticosteroids to the affected knee; AND

iii. The product is administered by or under the supervision of a physician specializing in rheumatology, orthopedic surgery, or physical medicine and rehabilitation (physiatrist).

B) Patient has Already Received One or More Courses of Hyaluronic Acid Derivative in the Same Knee. Approve ONE repeat course if the patient meets ALL of the following conditions (i, ii, and iii)

i. At least 6 months have elapsed since the last injection with any hyaluronic acid derivative; AND

ii. According to the prescriber, the patient had a response to the previous course of hyaluronic acid derivative therapy for osteoarthritis of the knee and now requires additional therapy for osteoarthritis symptoms; AND
Note: Examples of a response include reduced joint pain, tenderness, or morning stiffness, improved mobility.

iii. The product is administered by or under the supervision of a physician specializing in rheumatology, orthopedic surgery, or physical medicine and rehabilitation (physiatrist).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of hyaluronic acid derivatives is not recommended in the following situations:

18. Acute Ankle Sprain. A randomized, controlled, prospective trial was conducted which assessed the use of intraarticular hyaluronic acid in acute ankle sprains.[20-21] Patients treated with intraarticular hyaluronic acid (n = 79) within 48 hours of injury and again on Day 4 reported a time to pain-free and disability-free return to sport of 11 days (± 8 days) compared with 17 days (± 8 days) for placebo ($P < 0.05$).[18] All patients were also treated with standard of care (rest, ice, compression, and elevation [RICE]). At 24 months, the placebo group experienced an increase in repeat sprains when compared with those treated with an intraarticular hyaluronic acid product (21 recurrent ankle sprains in the placebo group compared with 7 recurrent ankle sprains in the HAD treatment group [$P < 0.001$]) as well as a significant difference in missed days from participation in sport activity (49 days vs. 12 days for the placebo and HAD groups, respectively; $P < 0.001$).[21] More data are needed to determine the role of intraarticular hyaluronic acid products in the treatment of acute ankle sprains.

19. **Osteoarthritis (OA) and Other Pathologic Conditions Involving Joints Other than the Knee** (e.g., hand, hip, ankle, shoulder OA, temporomandibular joint [TMJ], adhesive capsulitis of the shoulder, subacromial impingement). The prescribing information for these agents state in the precautions section that the safety and effectiveness of hyaluronic acid derivatives injections into joints other than the knee have not been established.[1-16] Due to the absence of evidence to support use of intraarticular hyaluronic acid and potential for harm, the guidelines for the management of hand, hip, and knee OA by American College of Rheumatology (2019) do not recommend use of intraarticular hyaluronic acid in patients with hand or hip OA.[17] Small trials have also investigated intraarticular hyaluronic acid in other joints, including ankle OA and hip OA.[23-38] More data are needed to determine if there is a role for intraarticular hyaluronic acid for the treatment of OA involving other joints. A small trial (n = 70) found that intraarticular hyaluronic acid did not result in increased benefit for adhesive capsulitis of the shoulder (also known as frozen shoulder) in patients who were already receiving physical therapy.[39] Another small study (n = 159) did not show benefit of intraarticular hyaluronic acid over corticosteroid or placebo injections in patients with subacromial impingement.[40]

20. **Pathologic Conditions of the Knee Other than Osteoarthritis** (e.g., chondromalacia patellae, osteochondritis dissecans, patellofemoral syndrome, post-anterior cruciate ligament [ACL] reconstruction). Intraarticular hyaluronic acid products are indicated in knee osteoarthritis.[1-16] Adequate, well-designed trials have not clearly established the use of intraarticular hyaluronic acid in other conditions of the knee.[41-42]

21. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Early annual revision	Add TriVisc and Visco-3 to the policy with the same criteria as other agents. Approval duration is for 1 month.	02/07/2018
Early annual revision	Add Synojoynt to the policy with the same criteria as other agents. Approval duration is for 1 month. Adjust approval duration for Euflexxa, Gelsyn-3, and Synvisc to approve for 1 month (previously was 5 weeks) which aligns with other products given as a course of three injections. Clarify that criteria for patients who have already received a course of a hyaluronic acid derivative intraarticular product applies to patients who have already received one or more courses of therapy.	10/31/2018
Early annual revision	Add Triluron to the policy with the same criteria as other agents. Approval duration is for 1 month. Throughout the policy, replace reference to Synojoynt with sodium	07/31/2019

	hyaluronate 1% (aligns with how product is marketed in the US). Remove Supartz from the policy (obsolete).	
Annual revision	**Osteoarthritis of the Knee**: Examples of radiographic evidence, non-steroidal anti-inflammatory drugs, and response to therapy were moved to notes in the criteria (previously listed as examples within the criteria). For the criteria applying to patients previously treated who have responded to therapy, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician).	08/26/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hyperlipidemia – Nexletol Prior Authorization Policy
- Nexletol™ (bempedoic acid tablets – Esperion)

REVIEW DATE: 03/04/2020

OVERVIEW

Nexletol, an adenosine triphosphate-citrate lyase inhibitor, is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of heterozygous familial hypercholesterolemia (HeFH) or established atherosclerotic cardiovascular disease (ASCVD) in adults who require additional lowering of low-density lipoprotein cholesterol (LDL-C). Limitations of Use. The effect of Nexletol on cardiovascular (CV) morbidity and mortality have not been established.

Disease Overview

ASCVD (including CV disease) is a leading cause of morbidity and mortality worldwide.[2-4] ASCVD is defined as patients who have experienced an acute coronary syndrome (ACS) event, those with a history of myocardial infarction (MI), stable or unstable angina or coronary or other revascularizations, stroke, transient ischemic attack, or peripheral arterial disease.[3,4] Lowering LDL-C levels has been strongly correlated to reduce the risk of subsequent CV disease among patients with ASCVD. However, many risk factors contribute to ASCVD including smoking, hypertension, obesity, physical inactivity, poor nutrition, and other clinical conditions (e.g., diabetes, metabolic syndrome). In 2017, CV disease was listed as the underlying cause of death in approximately 859,125 US patients.[2] In 2017, CHD was the leading causes of death attributable to CV disease in the US (42.6%), followed by stroke (17.0%), high blood pressure (10.5%), heart failure (9.4%), diseases of the arteries (2.9%) and other CV diseases (17.6%). When considered independently from CV disease, stroke led to 146,383 US deaths in 2017.

Familial hypercholesterolemia is an autosomal dominant genetic disease that is noted by markedly elevated LDL-C, often at a young age, and premature ASCVD.[5-8] The condition is often undiagnosed and untreated. It is estimated that 620,000 patients in the US have familial hypercholesterolemia which includes HeFH and homozygous familial hypercholesterolemia (HoFH). HeFH is the most common of the defects and occurs in approximately 1 in 200 to 1 in 500 patients. LDL-C levels in adults who are untreated usually are > 220 mg/dL. HoFH is less common (one in 1 million people) and is associated with extremely elevated LDL-C levels (400 mg/dL [untreated]). Diagnosis may be considered by genetic testing. However, because a substantial percentage of patients do not have an identifiable mutation, the condition is clinically diagnosed on the basis of a combination of physical findings, family history, early-onset ASCVD, and LDL-C levels. A LDL-C ≥ 190 mg/dL in adults suggests a diagnosis of HeFH. Patients may also have physical findings such as cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma). The Simon Broom criteria and the Dutch Lipid Clinical Network Criteria are also useful for diagnosis HeFH and examine various factors such as cholesterol level, the presence of clinical findings, family history, and genetic analysis. Treatment to manage LDL-C levels is needed to prevent CV disease from developing in these patients with statins recommended as first-line. Other therapies are also added to reduce LDL-C.

Guidelines

Many guidelines are available regarding the treatment of patients with dyslipidemia which include the management of HeFH and ASCVD.[3-5,9-12] For patients with elevated LDL-C, statins are the cornerstone of therapy and recommended first-line to be used at maximally tolerated doses due to the established benefits regarding the reduction of CV risks. Atorvastatin 40 mg to 80 mg once daily (QD) and rosuvastatin 20 mg to 40 mg QD are considered high-intensity statins as they achieve LDL-C lowering of ≥ 50%. Other statin regimens, including atorvastatin and rosuvastatin at lower doses are classified as moderate-intensity (LDL-C reductions of 30% to 49%) products and low-intensity agents (LDL-C reductions < 30%). The American Heart Association (AHA)/American College of Cardiology (ACC) guidelines on the management of blood cholesterol (2018) defines ACSVD as ACS, those with a history of MI, stable or unstable angina or coronary or other revascularizations, stroke, transient ischemic attack (TIA), or peripheral arterial disease (PAD).[2,3] An LDL-C < 70 mg/dL is recommended in for most patients with ASCVD to reduce CV risk.

In 2015 the AHA published a scientific statement regarding familial hypercholesterolemia. Key points are that the condition may start early (in childhood or adolescence) and is noted by LDL-C levels ≥ 190 mg/dL. Premature CV disease can result. Diagnosis can be confirmed by genetic testing. The Dutch Lipid Clinic Network Criteria and Simon Broome Criteria may also be used which incorporate cholesterol levels, family history, clinical findings, and physical manifestations. Aggressive lipid-lowering therapy is recommended to achieve LDL-C reductions of at least 50%. Statins are the initial treatment for all adults with familial hypercholesterolemia. High- or moderate-intensity statins are recommended; low potency statins are generally inadequate for patients with familial hypercholesterolemia due to the markedly elevated LDL-C levels. If LDL-C does not reach the desired goal or percentage decrease, ezetimibe is recommended to be added to statin therapy. Three drug combinations incorporating a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor, a bile acid sequestrant (colesevelam), or niacin is also recommended. For patients with HoFH, the addition of other therapies (e.g., Juxtapid® [lomitapide capsules], low-density lipoprotein apheresis) may be added. In patients with HeFH who have not yet manifested ASCVD, LDL-C levels ≤ 100 mg/dL are recommended.

In 2019 the AHA issued a scientific statement regarding statin safety and associated adverse events.[12] In general, statins are well-tolerated agents that have successfully led to decreased LDL-C levels which led to reductions in CV events (e.g., MI, ischemic stroke). The risk of serious statin-induced muscle injury (e.g., rhabdomyolysis) is low (< 0.01%). In US clinical practice, about 10% of patients stop taking statin therapy due to subjective complaints, of which muscle symptoms without significantly raised CK levels are noted. Data suggests that the muscle symptoms that occur among patients are not caused by the pharmacologic effects of the statin and restarting statin therapy for these patients is important, especially among patients at high risk of CV events, for whom CV event prevention is important. Several studies have shown that patients were believing that they were "statin intolerant". However, many patients were able to subsequently tolerate a statin upon rechallenge and receive the benefits provided with these agents. Other data supports this occurrence.[13-16]

Safety

Warnings/Precautions include hyperuricemia and an increased risk of tendon rupture.[1]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Nexletol. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nexletol is recommended in those who meet the following criteria:

FDA-Approved Indications

75. Atherosclerotic Cardiovascular Disease (ASCVD). Approve for 1 year if the patient meets the following criteria (A, B, and C):

A) The patient is ≥ 18 years of age; AND

B) The patient has had one of the following conditions or diagnoses (i, ii, iii, iv or v):

- **i.** The patient has had a previous myocardial infarction or has a history of an acute coronary syndrome; OR
- **ii.** The patient has a diagnosis of angina (stable or unstable); OR
- **iii.** The patient has a past history of stroke or transient ischemic attack; OR
- **iv.** The patient has peripheral arterial disease; OR
- **v.** The patient has undergone a coronary or other arterial revascularization procedure in the past (e.g., coronary artery bypass graft, percutaneous coronary intervention, angioplasty, coronary stent procedure); AND

C) The patient meets one of the following criteria (i or ii):

- **i.** The patient meets both of the following criteria (a and b):
  - **a)** The patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) AND ezetimibe (as a single-entity or as a combination product) concomitantly for ≥ 8 continuous weeks; AND
  - **b)** The low-density lipoprotein cholesterol level after this treatment regimen remains ≥ 70 mg/dL; OR
- **ii.** The patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):
  - **a)** The patient experienced statin-related rhabdomyolysis (Note: Statin-induced muscle breakdown that is usually associated with markedly elevated creatine kinase levels [at least 10 times the upper limit of normal], along with evidence of end organ damage which can include signs of acute renal injury [noted by substantial increases in serum creatinine {Scr}levels {a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr}] and/or myoglobinuria [myoglobin present in urine]); OR
  - **b)** The patient experienced skeletal-related muscle symptoms (e.g., myopathy [muscle weakness] or myalgia [muscle aches, soreness, stiffness, or tenderness]) and meets both of the following criteria [(1) and (2)]:
    - **(1)** The skeletal-related muscle symptoms (e.g., myopathy or myalgia) occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND
    - **(2)** When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms (e.g., myopathy, myalgia) resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin).

3. Heterozygous Familial Hypercholesterolemia (HeFH). Approve for 1 year if the patient meets the following criteria (A, B, and C):

53. The patient is ≥ 18 years of age; AND

54. The patient meets one of the following criteria (i, ii, iii, or iv):

- **i.** The patient has an untreated low-density lipoprotein cholesterol (LDL-C) level ≥ 190 mg/dL (prior to treatment with antihyperlipidemic agents); OR
- **ii.** The patient has genetic confirmation of HeFH by mutations in the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin kexin type 9 or low-density lipoprotein receptor adaptor protein 1 gene; OR
- **iii.** The patient has been diagnosed with HeFH meeting one of the following diagnostic criteria thresholds (a or b):
  - **a)** The prescriber used the Dutch Lipid Network criteria and the patient has a score > 5; OR

b) The prescriber used the Simon Broome criteria and the patient met the threshold for "definite" or "possible" familial hypercholesterolemia; OR

iv. The patient has clinical manifestations of HeFH (e.g., cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma); AND

55. The patient meets one of the following criteria (i or ii):

i. The patient meets both of the following criteria (a and b):

a) The patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) AND ezetimibe (as a single-entity or as a combination product) concomitantly for ≥ 8 continuous weeks; AND

b) The LDL-C level after this treatment regimen remains ≥ 70 mg/dL; OR

ii. The patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):

a) The patient experienced statin-related rhabdomyolysis (Note: Statin-induced muscle breakdown that is usually associated with markedly elevated creatine kinase levels [at least 10 times the upper limit of normal], along with evidence of end organ damage which can include signs of acute renal injury [noted by substantial increases in serum creatinine {Scr} levels {a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr}] and/or myoglobinuria [myoglobin present in urine]); OR

b) The patient experienced skeletal-related muscle symptoms (e.g., myopathy [muscle weakness] or myalgia [muscle aches, soreness, stiffness, or tenderness]) and meets both of the following criteria [(1) and (2)]:

(1) The skeletal-related muscle symptoms (e.g., myopathy or myalgia) occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND

(2) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms (e.g., myopathy, myalgia) resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nexletol is recommended in those who meet the following criteria:

91. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	03/04/2020
Update	3/25/2020: No criteria changes. For the diagnosis of ASCVD and HeFH, the criteria question was broken up into two sections as follows: **C.i.** The patient meets both of the following criteria (a and b): **a)** The patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) AND ezetimibe (as a single-entity or as a combination product) concomitantly for ≥ 8 continuous weeks; AND **b)** The LDL-C level after this treatment regimens remains ≥ 70 mg/dL.	--

ASCVD – Atherosclerotic cardiovascular disease; HeFH – Heterozygous familial hypercholesterolemia; LDL –C – Low-density lipoprotein cholesterol.

APPENDIX A.

Simon Broome Register Diagnostic Criteria[15]

Definite Familial Hypercholesterolemia:

a) Raised cholesterol
   (i) Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years;
   (ii) Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult (aged > 16 years);

b) AND
   (i) Tendon xanthomas in the patient or in a first (parent, sibling, or child) or second-degree relative (grandparent, aunt, or uncle);

c) OR
   (i) DNA-based evidence of LDL-receptor, familial defective apo B-100, or PCSK9 mutation.

Possible Familial Hypercholesterolemia:

a) Raised cholesterol
   (i) Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years;
   (ii) Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult;

b) AND at least one of the following:
   (i) Family history of premature myocardial infarction younger than 50 years of age in second-degree relative or younger than 60 years of age in first-degree relative;

c) OR
   (i) Family history of raised cholesterol > 7.5 mmol (290 mg/dL) in adult first-degree or second-degree relative or > 6.7 mmol/L (260 mg/dL) in child or sibling aged < 16 years.

APPENDIX B.
Dutch Lipid Network Criteria for Familial Hypercholesterolemia[16]

Criteria	Score
Family History	
First-degree relative with known premature coronary and/or vascular disease (men < 55 years, women < 60 years)	1
First degree relative with known LDL-C > 95th percentile for age and sex	1
First-degree relative with tendon xanthomata and/or arcus cornealis, OR	2
Children aged < 18 years with LDL-C > 95th percentile for age and sex	2
Clinical History	
Patient with premature CAD (age as above)	2
Patient with premature cerebral or peripheral vascular disease (age as above)	1
Physical Examination	
Tendon xanthomas	6
Arcus cornealis at age < 45 years	4
LDL-C	
LDL-C ≥ 8.5 mmol/L (330 mg/dL)	8
LDL-C 6.5 to 8.4 mmol/L (250 to 329 mg/dL)	5
LDL-C 5.0 to 6.4 mmol/L (190 to 249 mg/dL)	3
LDL-C 4.0 to 4.9 mg/dL (155 to 189 mg/dL)	1
DNA analysis	
Functional mutation LDLR, APOB or PCSK9 gene	8
Stratification	**Total score**
Definite familial hypercholesterolemia	> 8
Probable familial hypercholesterolemia	6 to 8
Possible familial hypercholesterolemia	3 to 5
Unlikely familial hypercholesterolemia	< 3

LDL-C – Low-density lipoprotein cholesterol; CAD – Coronary artery disease; LDLR – Low-density lipoprotein receptor; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

PRIOR AUTHORIZATION POLICY

POLICY: Hyperlipidemia – Nexlizet Prior Authorization Policy

- Nexlizet™ (bempedoic acid and ezetimibe tablets – Esperion)

REVIEW DATE: 04/01/2020

OVERVIEW
Nexlizet, contains bempedoic acid, an adenosine triphosphate-citrate lyase inhibitor, and ezetimibe, a cholesterol absorption inhibitor. It is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of heterozygous familial hypercholesterolemia (HeFH) or established atherosclerotic cardiovascular disease (ASCVD) in adults who require additional lowering of low-density lipoprotein cholesterol (LDL-C). Limitations of Use. The effect of Nexlizet on cardiovascular (CV) morbidity and mortality have not been established.

Disease Overview
ASCVD (including CV disease) is a leading cause of morbidity and mortality worldwide.[2-4] ASCVD is defined as patients who have experienced an acute coronary syndrome (ACS) event, those with a history of myocardial infarction (MI), stable or unstable angina or coronary or other revascularizations, stroke, transient ischemic attack, or peripheral arterial disease.[3,4] Lowering LDL-C levels has been strongly correlated to reduce the risk of subsequent CV disease among patients with ASCVD. However, many risk factors contribute to ASCVD including smoking, hypertension, obesity, physical inactivity, poor nutrition,

and other clinical conditions (e.g., diabetes, metabolic syndrome). In 2017, CV disease was listed as the underlying cause of death in approximately 859,125 US patients.[2] In 2017, CHD was the leading causes of death attributable to CV disease in the US (42.6%), followed by stroke (17.0%), high blood pressure (10.5%), heart failure (9.4%), diseases of the arteries (2.9%) and other CV diseases (17.6%). When considered independently from CV disease, stroke led to 146,383 US deaths in 2017.

Familial hypercholesterolemia is an autosomal dominant genetic disease that is noted by markedly elevated LDL-C, often at a young age, and premature ASCVD.[5-8] The condition is often undiagnosed and untreated. It is estimated that 620,000 patients in the US have familial hypercholesterolemia which includes HeFH and homozygous familial hypercholesterolemia (HoFH). HeFH is the most common of the defects and occurs in approximately 1 in 200 to 1 in 500 patients. LDL-C levels in adults who are untreated usually are > 220 mg/dL. HoFH is less common (one in 1 million people) and is associated with extremely elevated LDL-C levels (400 mg/dL [untreated]). Diagnosis may be considered by genetic testing. However, because a substantial percentage of patients do not have an identifiable mutation, the condition is clinically diagnosed on the basis of a combination of physical findings, family history, early-onset ASCVD, and LDL-C levels. A LDL-C ≥ 190 mg/dL in adults suggests a diagnosis of HeFH. Patients may also have physical findings such as cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma). The Simon Broom criteria and the Dutch Lipid Clinical Network Criteria are also useful for diagnosis HeFH and examine various factors such as cholesterol level, the presence of clinical findings, family history, and genetic analysis. Treatment to manage LDL-C levels is needed to prevent CV disease from developing in these patients with statins recommended as first-line. Other therapies are also added to reduce LDL-C.

Guidelines

Many guidelines are available regarding the treatment of patients with dyslipidemia which include the management of HeFH and ASCVD.[3-5,9-12] For patients with elevated LDL-C, statins are the cornerstone of therapy and recommended first-line to be used at maximally tolerated doses due to the established benefits regarding the reduction of CV risks. Atorvastatin 40 mg to 80 mg once daily (QD) and rosuvastatin 20 mg to 40 mg QD are considered high-intensity statins as they achieve LDL-C lowering of ≥ 50%. Other statin regimens, including atorvastatin and rosuvastatin at lower doses are classified as moderate-intensity (LDL-C reductions of 30% to 49%) products and low-intensity agents (LDL-C reductions < 30%). The American Heart Association (AHA)/American College of Cardiology (ACC) guidelines on the management of blood cholesterol (2018) defines ACSVD as ACS, those with a history of MI, stable or unstable angina or coronary or other revascularizations, stroke, transient ischemic attack (TIA), or peripheral arterial disease (PAD).[2,3] An LDL-C < 70 mg/dL is recommended in for most patients with ASCVD to reduce CV risk.

In 2015 the AHA published a scientific statement regarding familial hypercholesterolemia. Key points are that the condition may start early (in childhood or adolescence) and is noted by LDL-C levels ≥ 190 mg/dL. Premature CV disease can result. Diagnosis can be confirmed by genetic testing. The Dutch Lipid Clinic Network Criteria and Simon Broome Criteria may also be used which incorporate cholesterol levels, family history, clinical findings, and physical manifestations. Aggressive lipid-lowering therapy is recommended to achieve LDL-C reductions of at least 50%. Statins are the initial treatment for all adults with familial hypercholesterolemia. High- or moderate-intensity statins are recommended; low potency statins are generally inadequate for patients with familial hypercholesterolemia due to the markedly elevated LDL-C levels. If LDL-C does not reach the desired goal or percentage decrease, ezetimibe is recommended to be added to statin therapy. Three drug combinations incorporating a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor, a bile acid sequestrant (colesevelam), or niacin is also recommended. For patients with HoFH, the addition of other therapies (e.g., Juxtapid® [lomitapide capsules], low-density lipoprotein apheresis) may be added. In patients with HeFH who have not yet manifested ASCVD, LDL-C levels ≤ 100 mg/dL are recommended.

In 2019 the AHA issued a scientific statement regarding statin safety and associated adverse events.[12] In general, statins are well-tolerated agents that have successfully led to decreased LDL-C levels which led to reductions in CV events (e.g., MI, ischemic stroke). The risk of serious statin-induced muscle injury (e.g., rhabdomyolysis) is low (< 0.01%). In US clinical practice, about 10% of patients stop taking statin therapy due to subjective complaints, of which muscle symptoms without significantly raised CK levels are noted. Data suggests that the muscle symptoms that occur among patients are not caused by the pharmacologic effects of the statin and restarting statin therapy for these patients is important, especially among patients at high risk of CV events, for whom CV event prevention is important. Several studies have shown that patients were believing that they were "statin intolerant". However, many patients were able to subsequently tolerate a statin upon rechallenge and receive the benefits provided with these agents. Other data supports this occurrence.[13-16]

Safety

Warnings/Precautions include hyperuricemia and an increased risk of tendon rupture.[1]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Nexlizet. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nexlizet is recommended in those who meet the following criteria:

FDA-Approved Indication

76. Atherosclerotic Cardiovascular Disease (ASCVD). Approve for 1 year if the patient meets the following criteria (A, B, and C):

D) The patient is ≥ 18 years of age; AND

E) The patient has had one of the following conditions or diagnoses (i, ii, iii, iv or v):

- **i.** The patient has had a previous myocardial infarction or has a history of an acute coronary syndrome; OR
- **ii.** The patient has a diagnosis of angina (stable or unstable); OR
- **iii.** The patient has a past history of stroke or transient ischemic attack; OR
- **iv.** The patient has peripheral arterial disease; OR
- **v.** The patient has undergone a coronary or other arterial revascularization procedure in the past (e.g., coronary artery bypass graft, percutaneous coronary intervention, angioplasty, coronary stent procedure); AND

F) The patient meets one of the following criteria (i or ii):

- **i.** The patient meets both of the following criteria (a and b):
  - **a)** The patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND
  - **b)** The low-density lipoprotein cholesterol level after therapy regimen remains ≥ 70 mg/dL; OR
- **ii.** The patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):
  - **a)** The patient experienced statin-related rhabdomyolysis (Note: Statin-induced muscle breakdown that is usually associated with markedly elevated creatine kinase levels [at least 10 times the upper limit of normal], along with evidence of end organ damage which can include signs of acute renal injury [noted by substantial increases in serum creatinine {Scr}levels {a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr}] and/or myoglobinuria [myoglobin present in urine]); OR
  - **b)** The patient experienced skeletal-related muscle symptoms (e.g., myopathy [muscle weakness] or myalgia [muscle aches, soreness, stiffness, or tenderness]) and meets both of the following criteria [(1) and (2)]:
    - **(1)** The skeletal-related muscle symptoms (e.g., myopathy or myalgia) occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND
    - **(2)** When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms (e.g., myopathy, myalgia) resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin).

4. Heterozygous Familial Hypercholesterolemia (HeFH). Approve for 1 year if the patient meets the following criteria (A, B, and C):

56. The patient is ≥ 18 years of age; AND

57. The patient meets one of the following criteria (i, ii, iii, or iv):

- **i.** The patient has an untreated low-density lipoprotein cholesterol (LDL-C) level ≥ 190 mg/dL (prior to treatment with antihyperlipidemic agents); OR
- **ii.** The patient has genetic confirmation of HeFH by mutations in the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin kexin type 9 or low-density lipoprotein receptor adaptor protein 1 gene; OR
- **iii.** The patient has been diagnosed with HeFH meeting one of the following diagnostic criteria thresholds (a or b):
  - **a)** The prescriber used the Dutch Lipid Network criteria and the patient has a score > 5; OR
  - **b)** The prescriber used the Simon Broome criteria and the patient met the threshold for "definite" or "possible" familial hypercholesterolemia; OR
- **iv.** The patient has clinical manifestations of HeFH (e.g., cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma); AND

58. The patient meets one of the following criteria (i or ii):

- **i.** The patient meets both of the following criteria (a and b):
  - **c)** The patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND

d) The LDL-C level after this treatment regimen remains ≥ 70 mg/dL; OR

ii. The patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):

a) The patient experienced statin-related rhabdomyolysis (Note: Statin-induced muscle breakdown that is usually associated with markedly elevated creatine kinase levels [at least 10 times the upper limit of normal], along with evidence of end organ damage which can include signs of acute renal injury [noted by substantial increases in serum creatinine {Scr} levels {a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr}] and/or myoglobinuria [myoglobin present in urine]); OR

b) The patient experienced skeletal-related muscle symptoms (e.g., myopathy [muscle weakness] or myalgia [muscle aches, soreness, stiffness, or tenderness]) and meets both of the following criteria [(1) and (2)]:

(1) The skeletal-related muscle symptoms (e.g., myopathy or myalgia) occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND

(2) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms (e.g., myopathy, myalgia) resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nexlizet is recommended in those who meet the following criteria:

92. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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276. Rosenson RS, Baker S, Banach M, et al. Optimizing cholesterol treatment in patients with muscle complaints. *J Am Coll Cardiol*. 2017;70(10):1290-1301.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/01/2020

APPENDIX A.

Simon Broome Register Diagnostic Criteria[15]

Definite Familial Hypercholesterolemia:

a) Raised cholesterol
   (i) Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years;
   (ii) Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult (aged > 16 years);

b) AND
   (i) Tendon xanthomas in the patient or in a first (parent, sibling, or child) or second-degree relative (grandparent, aunt, or uncle);

c) OR
   (ii) DNA-based evidence of LDL-receptor, familial defective apo B-100, or PCSK9 mutation.

Possible Familial Hypercholesterolemia:

a) Raised cholesterol
   (i) Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years;
   (ii) Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult;

b) AND at least one of the following:
   (i) Family history of premature myocardial infarction younger than 50 years of age in second-degree relative or younger than 60 years of age in first-degree relative;

c) OR
   (i) Family history of raised cholesterol > 7.5 mmol (290 mg/dL) in adult first-degree or second-degree relative or > 6.7 mmol/L (260 mg/dL) in child or sibling aged < 16 years.

APPENDIX B.
Dutch Lipid Network Criteria for Familial Hypercholesterolemia[16]

Criteria	Score
Family History	
First-degree relative with known premature coronary and/or vascular disease (men < 55 years, women < 60 years)	1
First degree relative with known LDL-C > 95th percentile for age and sex	1
First-degree relative with tendon xanthomata and/or arcus cornealis, OR	2
Children aged < 18 years with LDL-C > 95th percentile for age and sex	2
Clinical History	
Patient with premature CAD (age as above)	2
Patient with premature cerebral or peripheral vascular disease (age as above)	1
Physical Examination	
Tendon xanthomas	6
Arcus cornealis at age < 45 years	4
LDL-C	
LDL-C ≥ 8.5 mmol/L (330 mg/dL)	8
LDL-C 6.5 to 8.4 mmol/L (250 to 329 mg/dL)	5
LDL-C 5.0 to 6.4 mmol/L (190 to 249 mg/dL)	3
LDL-C 4.0 to 4.9 mg/dL (155 to 189 mg/dL)	1
DNA analysis	
Functional mutation LDLR, APOB or PCSK9 gene	8
Stratification	**Total score**
Definite familial hypercholesterolemia	> 8
Probable familial hypercholesterolemia	6 to 8
Possible familial hypercholesterolemia	3 to 5
Unlikely familial hypercholesterolemia	< 3

LDL-C – Low-density lipoprotein cholesterol; CAD – Coronary artery disease; LDLR – Low-density lipoprotein receptor; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

PRIOR AUTHORIZATION POLICY

POLICY: Hyperlipidemia – Omega-3 Fatty Acid Products
- Lovaza® (omega-3-acid ethyl esters capsules – GlaxoSmithKline, generic)
- Vascepa® (icosapent ethyl capsules – Amarin, generic)

REVIEW DATE: 01/13/2021

OVERVIEW
Lovaza, a combination of ethyl esters of omega-3 fatty acids (mainly eicosapentaenoic acid [EPA and docosahexaenoic acid [DHA]) and Vascepa, an esthyl ester of EPA, are indicated for:[1,2]

- **Hypertriglyceridemia** (severe, triglyceride [TG] levels ≥ 500 mg/dL), to reduce TG levels as an adjunct to diet in adults.

Vascepa is also indicated to:[2,3]

- **Reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina** requiring hospitalization in adults with elevated TG levels (≥ 150 mg/dL) and either established cardiovascular (CV) disease or diabetes mellitus with two or more additional risk factors for CV disease, as an adjunct to maximally tolerated statin therapy.

Lovaza and Vascepa have been studied in patients with TG levels ≥ 200 mg/dL and < 500 mg/dL in patients who had persistently high TGs despite treatment with statin therapy and proper dietary modifications.[4,5] In these short-term trials lasting 6 to 12 weeks in duration, the addition of omega-3 fatty acid therapy led to further reductions in TG levels.

Guidelines/Scientific Statements

Several guidelines are available that discuss the management of elevated TG values and have incorporated omega-3 fatty acid products.[6-11] Highlights from a few guidelines are below.

- The **American Diabetes Association Standards of Care** regarding CV disease and risk management (2021) state that Vascepa should be considered for patients with diabetes and atherosclerotic cardiovascular disease (ASCVD) or other cardiac risk factors on a statin with controlled low-density lipoprotein cholesterol levels, but with elevated TG levels (135 to 499 mg/dL) to reduce CV risk.[10]
- The **National Lipid Association** (NLA) published a scientific statement regarding Vascepa (2019).[11] Based on the REDUCE-IT trial, the NLA position is that for patients ≥ 45 years of age with clinical ASCVD, or ≥ 50 years of age with diabetes mellitus requiring medication plus at least one additional risk factor, with fasting TG levels of 135 to 499 mg/dL on high-intensity or maximally tolerated statin therapy (with or without ezetimibe), treatment with Vascepa is recommended for ASCVD risk reduction (Class I evidence rating).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of omega-3 fatty acid products (Lovaza and Vascepa [both brand and generic]). All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of **Vascepa** (brand and generic) is recommended in those who meet the following criteria:

FDA-Approved Indication

15. Cardiovascular Risk Reduction in Patients with Elevated Triglycerides. Approve Vascepa (brand or generic) for 3 years if the patient meets all of the following criteria (A, B and C):

A) Patient meets one of the following (i or ii):

i. Patient has established cardiovascular disease; OR

Note: Examples of cardiovascular disease include a previous myocardial infarction (MI); a history of an acute coronary syndrome (ACS) event; angina (stable or unstable); past history of stroke or transient ischemic attack (TIA); peripheral arterial disease (PAD); or the patient has undergone a coronary or other arterial revascularization procedure in the past (e.g., coronary artery bypass graft [CABG], percutaneous coronary intervention [PCI], angioplasty, coronary stent procedure); OR

ii. Patient meets both of the following (a and b):

a) Patient has diabetes; AND

b) According to the prescriber, has at least two additional risk factors for cardiovascular disease.

Note: Examples of risk factors for cardiovascular disease include hypertension; low high-density lipoprotein cholesterol (HDL-C) levels (e.g., ≤ 40 mg/dL); renal dysfunction (creatinine clearance < 60 mL/min); family history of premature coronary disease; presence of

albuminuria; current cigarette smoking; familial hypercholesterolemia; and increased weight (body mass index greater than 25 kg/m^2); AND

B) Prior to initiation of therapy, the patient has a fasting baseline triglyceride level ≥ 150 mg/dL; AND

C) Patient meets one of the following criteria (i or ii):

i. Patient is receiving statin therapy; OR

ii. According to the prescriber the patient cannot tolerate statin therapy.

II. Coverage of **Lovaza** and **Vascepa** (both brand and generic) is recommended in those who meet the following criteria:

FDA-Approved Indication

16. Hypertriglyceridemia with Triglyceride (TG) Levels ≥ 500 mg/dL. Approve Lovaza or Vascepa (both brand or generic) for 3 years if the patient meets the following criteria (A and B):

A) Prior to initiation of therapy, the patient has a fasting baseline triglyceride (TG) level ≥ 500 mg/dL; AND

B) Patient has tried, or is currently receiving, one of the following products: niacin (immediate-release or extended-release), a fibrate, or a statin.

Note: Examples of fibrates include gemfibrozil, fenofibrate and fenofibric acid. Examples of statins include atorvastatin, rosuvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, and Livalo® (pitavastatin tablets). Also, a patient who requests Vascepa may potentially be reviewed under the criteria for Cardiovascular Risk Reduction in Patients with Elevated Triglycerides.

Other Uses with Supportive Evidence

17. Hypertriglyceridemia with Triglyceride (TG) Levels of 150 mg/dL to < 500 mg/dL. Approve Lovaza or Vascepa (both brand or generic) for 3 years if the patient meets the following criteria (A and B):

A) Prior to initiation of therapy, the patient has a fasting baseline triglyceride (TG) level of 150 mg/dL to < 500 mg/dL; AND

B) Patient has tried, or is currently receiving, one of the following products: niacin (immediate-release or extended-release), a fibrate, or a statin.

Note: Examples of fibrates include gemfibrozil, fenofibrate and fenofibric acid. Examples of statins include atorvastatin, rosuvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, and Livalo® (pitavastatin tablets). Also, a patient who requests Vascepa may potentially be reviewed under the criteria for Cardiovascular Risk Reduction in Patients with Elevated Triglycerides.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lovaza and Vascepa (both brand and generic) is not recommended in the following situations:

37. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Hypertriglyceridemia with Triglyceride (TG) Levels ≥ 500 mg/dL:** The option of inadequate efficacy according to the prescribing information of one over-the counter (OTC) omega-3 fatty acid product was removed. **Hypertriglyceridemia with Triglyceride (TG) Levels of 150 mg/dL to < 500 mg/dL:** The option of inadequate efficacy according to the prescribing information of one over-the counter (OTC) omega-3 fatty acid product was removed.	05/08/2019
Early Annual Revision	New criteria were added for the recent FDA-approved indication for Vascepa that addresses its use for "Cardiovascular Risk Reduction in Patients with Elevated Triglycerides". For the FDA-approved indication for Vascepa and Lovaza regarding "Hypertriglyceridemia with Triglyceride (TG) Levels ≥ 500 mg/dL" and the criteria under "Other Uses with Supportive Evidence" that addresses "Hypertriglyceridemia with Triglyceride (TG) Levels of 150 mg/dL to < 500 mg/dL" a note was added that patients requesting Vascepa may potentially be reviewed under those criteria. Also, wording was revised for these two indications to remove the word "pretreatment" and replace it with the phrase "prior to requesting Vascepa or Lovaza".	1/15/2020
Update	3/5/2020: No criteria changes. The title Hyperlipidemia was added to the name of the policy.	--
Annual Revision	It was cited that generic products to Vascepa are available. Also, the following changes were made: **Hypertriglyceridemia with Triglyceride (TG) Levels ≥ 500 mg/dL:** The examples of fibrates and statins were moved from the criteria to a Note. **Hypertriglyceridemia with Triglyceride (TG) Levels of 150 mg/dL to < 500 mg/dL:** The examples of fibrates and statins were moved from the criteria to a Note.	01/13/2021

TG – Triglyceride; OTC – Over-the-counter; FDA – Food and Drug Administration.

PRIOR AUTHORIZATION POLICY

POLICY: Hypoactive Sexual Desire Disorder – Addyi Prior Authorization Policy

- Addyi™ (flibanserin tablets – Sprout Pharmaceuticals)

REVIEW DATE: 12/16/2020

OVERVIEW

Addyi is indicated for the **treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD)** that is characterized by low sexual desire that causes marked distress or interpersonal difficulty and is NOT due to a co-existing medical or psychiatric condition; problems within the relationship; or the effects of a medication or other drug substance.[1] Acquired HSDD refers to HSDD that develops in a patient who previously had no problems with sexual desire. Generalized HSDD refers to HSDD that occurs regardless of the type of stimulation, situation, or partner. Addyi is not indicated for the treatment of HSDD in postmenopausal women or in men. It is also not indicated to enhance sexual performance.

Addyi is a centrally-acting post-synaptic serotonin 1A receptor agonist and a serotonin 2A receptor antagonist.[1] It has been shown to regulate levels of dopamine and norepinephrine and to induce transient decreases in serotonin levels in specific regions of the brain.[1,2] The exact mechanism of action of Addyi in the treatment of HSDD is not known.[1] According to the prescribing information, Addyi should be discontinued after 8 weeks if the patient does not report an improvement in her HSDD symptoms.

The prescribing information notes that Addyi should be discontinued after 8 weeks if the patient does not report any improvement in HSDD symptoms.[1] In the Addyi clinical studies, one of the coprimary efficacy endpoints was assessed by the median increase in the number of satisfying sexual events standardized over

a 28-day period. Since this is an objective measure of efficacy, it is used in the criteria to assess Addyi efficacy during initial therapy.

Safety

Addyi contains a Boxed Warning regarding the use of alcohol and the increase in risk of severe hypotension and syncope.[1] Patients should be counseled to wait at least two hours after consuming one or two standard alcoholic drinks before taking Addyi or skip the dose if they have consumed three or more standard alcoholic drinks that evening.

Guidelines

The American College of Obstetricians and Gynecologists (ACOG) guideline on Female Sexual Dysfunction (2019) notes the importance of recognizing if the loss of sexual interest is due to a co-morbid or undiagnosed condition, or medication.[5] Consultation with or referral to a mental health specialist with expertise and training in the treatment of female sexual dysfunction (e.g., sex therapists, psychologists, marriage/relationship counselors) should be considered based on the physician's level of expertise and the patient's individual needs. The guidelines note that Addyi was approved in 2015 by the FDA to treatment hypoactive sexual desire disorder in premenopausal women without depression. Addyi is noted as a treatment option for HSDD in premenopausal women without depression who are appropriately counseled about the risk of alcohol use during treatment.[5] The guidelines also discuss that systemic review and meta-analysis of existing studies with Addyi show that although the studies were randomized, their overall quality of evidence for efficacy and safety was very low.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Addyi. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Addyi is recommended in those who meet the following criteria:

FDA-Approved Indications

5. Hypoactive Sexual Desire Disorder (HSDD)/Female Sexual Interest/Arousal Disorder (FSIAD).

59. Initial Therapy. Approve for 8 weeks if the patient meets the following criteria (i, ii, iii, iv, v, and vi):

- **i.** Patient is premenopausal; AND
- **ii.** Patient's symptoms of HSDD/FSIAD have persisted for a minimum of 6 months; AND
- **iii.** Patient has had normal sexual desire in the past, prior to the diagnosis of HSDD/FSIAD; AND
- **iv.** Patient does **not** have a diagnosis of depression; AND
- **v.** Other known causes of HSDD/FSIAD, such as co-existing medical or psychiatric conditions, problems within a relationship, effects of medications (e.g., antidepressants), or drug abuse have been ruled out by the prescriber; AND
- **vi.** The prescriber has counseled the patient regarding the interaction with alcohol and Addyi, and the increased risk of hypotension and syncope.

60. Patient is Currently Receiving Addyi. Approve for 6 months if the patient meets the following criteria (i, ii, and iii):

- **i.** Patient is premenopausal; AND

ii. The prescriber confirms that since initiating Addyi therapy, the patient reports a significant improvement in sexual desire and/or a decrease in sexual distress; AND

iii. Patient has not reported any serious or concerning adverse events (e.g., hypotension, syncope, dizziness) while taking Addyi.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Addyi is not recommended in the following situations:

38. **Postmenopausal Patients.** Two published Phase III trials assessed the efficacy of Addyi in postmenopausal women with HSDD.[3-4] In the SNOWDROP trial though there was statistical significance in the primary endpoints (number of satisfying sexual events over 28 days and increase in desire score), the treatment difference between Addyi and placebo was very minimal.[3] The PLUMERIA study was discontinued early by the study sponsor for commercial reasons; however, published data are available for up to Week 16.[4] The improvement from baseline to Week 16 in the Female Sexual Function Index desire domain was significantly greater with Addyi compared with placebo, but the other co-primary endpoint of sexually satisfying events was not significantly different between Addyi and placebo. Addyi is currently not approved for use in postmenopausal women with HSDD/FSIAD symptoms.

39. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes	08/09/2017
Annual Revision	No criteria changes	08/22/2018
Annual Revision	Hypoactive Sexual Desire Disorder (HSDD)/Female Sexual Interest/Arousal Disorder (FSIAD), Initial Criteria: "Premenopausal" was removed from the indication and it was added to the criteria that the patient is premenopausal. The following criteria were added: 1) the patient's symptoms of HSDD/FSIAD have persisted for a minimum of 6 months; 2) the patient does not have a diagnosis of depression; 3) if the patient is currently taking an anti-depressant for a diagnosis other than depression, the prescriber has determined the medication is not contributing to HSDD/FSIAD; and 4) the situation of "problems in a relationship" were added as an example of the criteria that requires other known causes of HSDD/FSIAD have been ruled out. Hypoactive Sexual Desire Disorder (HSDD)/Female Sexual Interest/Arousal Disorder (FSIAD), Continuation Criteria: "Premenopausal" was removed from the indication and it was added to the criteria that the patient is premenopausal. The descriptor of "significant"	08/14/2019

	was added to the criteria that describes the increase in number of satisfying sexual events. The duration of approval for continuation therapy was changed from 12 months to 6 months. Conditions Not Recommended for Approval: The wording of the condition of "HSDD/FSIAD" in postmenopausal women was changed to just state "Postmenopausal Patients".	
Selected Revision	Removal of "The prescriber has evaluated and confirmed the patient's ability to abstain from alcohol use during treatment with Addyi" from initial therapy criteria. Removal of "The prescriber has confirmed that the patient continues to abstain from alcohol while on Addyi therapy" from continuation therapy criteria.	11/6/2019
Early Annual Revision	Hypoactive Sexual Desire Disorder (HSDD)/Female Sexual Interest/Arousal Disorder (FSIAD): • Removal of "if the patient is currently taking an antidepressant for a diagnosis other than depression, the prescriber has determined the medication is not contributing to HSDD/FSIAD." • Addition of "e.g., antidepressants" to other known causes of HSDD/FSIAD being ruled out by the prescriber. • Removal of criteria relating to pre-treatment number of satisfying sexual events. • Continuation of therapy criteria was updated to reporting a significant improvement in sexual desire and/or a decrease in sexual distress.	12/11/2019
Annual Revision	No criteria changes	12/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Hypoactive Sexual Desire Disorder – Vyleesi Prior Authorization Policy
- Vyleesi™ (bremelanotide subcutaneous injection – AMAG Pharmaceuticals, Inc.)

REVIEW DATE: 12/16/2020

OVERVIEW

Vyleesi is indicated for the **treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD)** as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is NOT due to: a co-existing medical or psychiatric condition, problems with the relationship, or effects of a medication or drug substance. Limitations of Use: Vyleesi is not indicated for the treatment of HSDD in postmenopausal women or in men. Vyleesi is not indicated to enhance sexual performance.[1] Acquired HSDD refers to HSDD that develops in a patient who previously had no problems with sexual desire. Generalized HSDD refers to HSDD that occurs regardless of the type of stimulation, situation, or partner.

In Vyleesi pivotal studies, patients were excluded if they were diagnosed with or being treated for depression, psychosis, bipolar disorder, or substance abuse within 6 months before screening.[2]

The prescribing information for Vyleesi notes that it should be discontinued after 8 weeks if the patient does not report an improvement in her symptoms.[1]

Guidelines

The American College of Obstetricians and Gynecologists (ACOG) guideline on Female Sexual Dysfunction (2019) notes the importance of recognizing if the loss of sexual interest is due to a co-morbid or undiagnosed condition, or medication.[3] Consultation with or referral to a mental health specialist with expertise and training in the treatment of female sexual dysfunction (e.g., sex therapists, psychologists, marriage/relationship counselors) should be considered based on the physician's level of expertise and the patient's individual needs. The guideline does not address Vyleesi, but note that Addyi (flibanserin tablet) was approved in 2015 by the FDA to treatment hypoactive sexual desire

disorder in premenopausal women without depression.[3] Addyi is noted as a treatment option for HSDD in premenopausal women without depression who are appropriately counseled about the risk of alcohol use during treatment.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vyleesi. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vyleesi is recommended in those who meet the following criteria:

FDA-Approved Indications

77. Hypoactive Sexual Desire Disorder (HSDD)/Female Sexual Interest/Arousal Disorder (FSIAD).

A) Initial Therapy. Approve for 8 weeks if the patient meets the following criteria (i, ii, iii, iv, and v):
- **i.** Patient is premenopausal; AND
- **ii.** Patient's symptoms of HSDD/FSIAD have persisted for a minimum of 6 months; AND
- **iii.** Patient has had normal sexual desire in the past, prior to the diagnosis of HSDD/FSIAD; AND
- **iv.** Patient has not been diagnosed or treated with depression within the previous 6 months; AND
- **v.** Other known causes of HSDD/FSIAD, such as co-existing medical or psychiatric conditions, problems within a relationship, effects of medications (e.g., antidepressants), or drug abuse have been ruled out by the prescriber.

B) Patient is Currently Receiving Vyleesi. Approve for 6 months if patient meets the following criteria (i and ii):
- **i.** Patient is premenopausal; AND
- **ii.** The prescriber confirms that since initiating Vyleesi therapy, the patient reports a significant improvement in sexual desire and/or a decrease in sexual distress.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vyleesi is not recommended in the following situations:

93. Postmenopausal Patients. Pivotal trials for Vyleesi included only premenopausal women with acquired, generalized hypoactive sexual desire disorder.[1]

94. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
New policy	--	08/14/2019

Early Annual Revision	Hypoactive Sexual Desire Disorder (HSDD)/Female Sexual Interest/Arousal Disorder (FSIAD): • Criteria was updated to "the patient has not been diagnosed or treated for depression within the previous 6 months;" previously criteria was "the patient does not have depression". • Removal of "if the patient is currently taking an antidepressant for a diagnosis other than depression, the prescriber has determined the medication is not contributing to HSDD/FSIAD." • Addition of "e.g., antidepressants" to other known causes of HSDD/FSIAD being ruled out by the prescriber. • Removal of criteria relating to pre-treatment number of satisfying sexual events. • Continuation of therapy criteria was updated to reporting a significant improvement in sexual desire and/or a decrease in sexual distress.	12/11/2019
Annual Revision	No criteria changes	12/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Idiopathic Pulmonary Fibrosis and Related Lung Disease – Esbriet Prior Authorization Policy
- Esbriet® (pirfenidone capsules – Genentech)

REVIEW DATE: 10/21/2020

OVERVIEW
Esbriet, a pyridine, is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).[1]

Disease Overview
IPF is a form of chronic interstitial lung pneumonia associated with histologic pattern of usual interstitial pneumonia (UIP).[8] The condition is specific for patients that have clinical features and the histologic pattern of IUP or a classical high-resolution computed tomography (HRCT) scan for IPF. In this lung condition there is cellular proliferation, interstitial inflammation, fibrosis, or the combination of these findings, within the alveolar wall that is not due to infection or cancer.[9] IPF is rather rare and the prevalence in the US ranges from 10 to 60 cases per 100,000. However, in one study, the prevalence was 494 cases per 100,000 in 2011 in adults > 65 years of age, which is higher than previous information. The disease mainly impacts older adults.[8] Symptoms include a progressive dry cough and exertional dyspnea. Patients experience a high disease burden with hospital admissions. The clinical course varies among patients but the mean survival after symptom onset is usually 3 to 5 years. The cause is unknown but environmental and occupational hazards may play a role, as well as a history of smoking. Medical therapy is only modestly effective and mainly shows the rate of disease progression. Agents FDA-approved for IPF are Ofev® (nintedanib capsules) and Esbriet. Lung transplantation is a therapeutic option.

Clinical Efficacy
The efficacy of Esbriet was assessed in patients with IPF in three Phase III, randomized, double-blind, placebo-controlled, multicenter, multinational trials (n = 1,247).[1-3] In ASCEND (Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis),[1,2] and CAPACITY 004 (Clinical Studies Assessing Pirfenidone in idiopathic pulmonary fibrosis: Research of Efficacy and Safety Outcomes)[1,3] patients were required to have a percent predicted forced vital capacity (%FVC) ≥ 50% at

baseline. Esbriet 2,403 mg/day led to a statistically significant treatment effect regarding the primary efficacy analysis for the change in the %FVC over the study duration of 52 weeks and 72 weeks, respectively. Also, a reduction in the mean decline in forced vital capacity (in mL) was observed in both studies for patients receiving Esbriet 2,403 mg/day compared with placebo.[1-3] Some information suggests that patients who have %FVC < 50% may also have some benefits from therapy.[10-13]

Guidelines

In 2015, the clinical practice guideline from the American Thoracic Society (ATS), European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT) on the treatment of idiopathic pulmonary fibrosis were updated.[4] Regarding Esbriet, the guideline suggests use of this medication (conditional recommendation, moderate confidence in estimates of effect). The guideline notes that the data with Esbriet cannot be generalized to patients with IPF who have more severe impairment of pulmonary function tests or for patients with other significant comorbidities.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Esbriet. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Esbriet, initial approval requires Esbriet to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Esbriet is recommended in those who meet the following criteria:

FDA-Approved Indication

6. Idiopathic Pulmonary Fibrosis (IPF). Approve if the patient meets the following criteria (A, B, C, and D).
- **61.** Patient is ≥ 40 years of age; AND
- **62.** Forced vital capacity (FVC) is ≥ 40% of the predicted value; AND
- **63.** Diagnosis of IPF is confirmed by one of the following (i or ii):
  - **i.** Findings on high-resolution computed tomography (HRCT) indicates usual interstitial pneumonia (UIP); OR
  - **ii.** A surgical lung biopsy demonstrates usual interstitial pneumonia (UIP); AND
- **64.** Medication is prescribed by, or in consultation with, a pulmonologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Esbriet is not recommended in the following situations:

40. Esbriet is Being Used Concomitantly with Ofev® (nintedanib capsules). Ofev is another medication indicated for the treatment of IPF. The effectiveness and safety of concomitant use of Esbriet with Ofev have not been established. The 2015 ATS/ERS/JRS, ALAT clinical practice guideline regarding the treatment of idiopathic pulmonary fibrosis (an update of the 2011 clinical practice guidelines) do not recommend taking Ofev and Esbriet in combination.[4] A small exploratory study was done in which patients with IPF receiving Ofev added on Esbriet.[7] Further research is needed to determine the utility of this combination regimen.

41. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	12/12/2018
Early Annual Revision	The Policy header was changed to add the description "and Related Lung Disease" to the Idiopathic Pulmonary Fibrosis title. Also, the following criteria changes were made: **1. Idiopathic Pulmonary Fibrosis:** The forced vital capacity threshold was changed from ≥ 50% to ≥ 40%. Previously, only the baseline (before initiation of therapy) values were accepted but now the timing of the assessment is not specified.	10/02/2019
Annual Revision	No criteria changes.	10/21/2020

PRIOR AUTHORIZATION POLICY

POLICY: Idiopathic Pulmonary Fibrosis and Related Lung Disease – Ofev Prior Authorization Policy

- Ofev® (nintedanib capsules – Boehringer Ingelheim)

REVIEW DATE: 10/21/2020

OVERVIEW

Ofev, a kinase inhibitor, is indicated for the following uses:[1]

- Treatment of **chronic fibrosing interstitial lung disease** with a progressive phenotype.

- Treatment of **idiopathic pulmonary fibrosis** (IPF).
- Slowing the rate of decline in pulmonary function in patients with **systemic sclerosis-associated interstitial lung disease**.

Disease Overview
IPF is a form of chronic interstitial lung pneumonia associated with histologic pattern of usual interstitial pneumonia (UIP).[8] The condition is specific for patients that have clinical features and the histologic pattern of IUP or a classical high-resolution computed tomography (HRCT) scan for IPF. In this lung condition there is cellular proliferation, interstitial inflammation, fibrosis, or the combination of these findings, within the alveolar wall that is not due to infection or cancer.[9] IPF is rather rare and the prevalence in the US ranges from 10 to 60 cases per 100,000. However, in one study, the prevalence was 494 cases per 100,000 in 2011 in adults > 65 years of age, which is higher than previous information. The disease mainly impacts older adults.[8] Symptoms include a progressive dry cough and exertional dyspnea. Patients experience a high disease burden with hospital admissions. The clinical course varies among patients but the mean survival after symptom onset is usually 3 to 5 years. The cause is unknown but environmental and occupational hazards may play a role, as well as a history of smoking. Medical therapy is only modestly effective and mainly shows the rate of disease progression. Agents FDA-approved for IPF are Ofev and Esbriet® (pirfenidone capsules and film-coated tablets). Lung transplantation is a therapeutic option.

Interstitial lung disease is a common manifestation of systemic sclerosis and is a leading cause of death.[11-13] Among patients who have systemic sclerosis, up to one-half of patients may have interstitial lung disease.[17] The estimate prevalence and annual incidence of systemic sclerosis-associated interstitial lung disease is 1.7 to 4.2 and 0.1 to 0.4 per 100,000 individuals, respectively.[17] However, it is notable that systemic sclerosis is a connective disease that it not limited to the lungs but impacts the skin, blood vessels, heart, kidneys, gastrointestinal tract, and musculoskeletal system. The condition displays great heterogeneity and can be challenging to treat.[11] When the disease affects the internal organs, significant morbidity and mortality may result. Mycophenolate, cyclophosphamide, and azathioprine are immunosuppressants that are utilized in the treatment of interstitial lung disease associated with systemic sclerosis. Corticosteroids are also used. Ofev is the first medication specifically indicated for this use.[1]

Clinical Efficacy
The clinical efficacy of Ofev if patients with IPF was established in one Phase II study and two Phase III studies that were identical in design (n = 1,231).[1-3] The trials were randomized, double-blind, placebo-controlled studies comparing treatment with Ofev 150 mg BID with placebo for 52 weeks. In the two Phase III studies, patients were ≥ 40 years of age and had a forced vital capacity (FVC) ≥ 50% of the predicted value. The diagnosis was confirmed by HRCT and, if available, surgical lung biopsy specimens were assessed. For all three studies, a statistically significant reduction in the annual rate of decline of FVC was observed in patients receiving Ofev compared with patients receiving placebo. Also, data shows that the proportion of patients that demonstrated categorical declines in lung function was lower for patients given Ofev compared with placebo. Acute IPF exacerbations were also reduced.[1-3] Some information suggests that patients who have FVC < 50% of predicted may also have some benefits from therapy.[14-16]

The efficacy of Ofev was established in SENSCIS, a randomized, double-blind, placebo-controlled Phase III trial in patients ≥ 18 years of age with systemic sclerosis-related interstitial lung disease (n = 576).[1,12] Patients were randomized to Ofev or placebo for at least 52 weeks and up to 100 weeks. Patients had ≥ 10% fibrosis on a chest HRCT scan conducted within the previous 12 months and had an FVC ≥ 40% of predicted. The primary efficacy endpoint was the annual rate of decline in FVC over 52 weeks. The annual rate of decline of FVC over 52 weeks was significantly reduced by 41 mL in patients receiving Ofev vs. placebo (-52 mL for Ofev vs. -93 mL with placebo).

The efficacy of Ofev was assessed in patients ≥ 18 years of age with chronic fibrosis interstitial lung diseases with a progressive phenotype in a Phase III, double-blind, placebo-controlled trial (INBUILD) [n = 663].[1,18,19] Patients receiving Ofev 150 mg BID or placebo for at least 52 weeks and the main endpoint was the annual rate in decline in FVC over 52 weeks. Patients who had a clinical diagnosis of chronic fibrosing interstitial lung disease were involved in the trial if they had relevant fibrosis (greater than 10% fibrotic features) and had clinical signs of progression (e.g., FVC decline ≥ 10%, recent FVC decline ≥ 5% but < 10% with worsening symptoms or imaging, or worsening symptoms and worsening imaging). Patients were required to have an FVC ≥ 45% of predicted and a diffusing capacity of the lung for carbon monoxide of at least 30% and < 80% of predicted.

Guidelines

In 2015, the clinical practice guideline from the American Thoracic Society (ATS), European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT) on the treatment of IPF were updated.[4] Regarding Ofev, the guideline suggests use of this medication (conditional recommendation, moderate confidence in estimates of effect). The guideline notes that the data with Ofev focuses on patients with IPF who have mild to moderate impairment in pulmonary function tests. It is not known if the benefits would differ among patients with more severe impairment in pulmonary function testing or in patients who have other comorbidities.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ofev. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ofev in many of the conditions, approval requires Ofev to be prescribed by or in consultation with a physician who specializes in the condition being treated in several indications.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ofev is recommended in those who meet the following criteria:

FDA-Approved Indications

7. **Chronic Fibrosing Interstitial Lung Disease.** Approve for 3 years if the patient meets the following criteria (A, B, C and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Forced vital capacity is ≥ 45% of the predicted value; AND
   - **C)** According to the prescriber the patient has fibrosing lung disease impacting more than 10% of lung volume on high-resolution computed tomography; AND
   - **D)** According to the prescriber the patient has clinical signs of progression.

   Note: Examples of clinical signs of progression include a forced vital capacity decline ≥ 10% of the predicted value or forced vital capacity decline ≥ 5% to < 10% with worsening symptoms and/or worsening imaging.

   Note: Examples of conditions include hypersensitivity pneumonitis; idiopathic non-specific interstitial pneumonitis; idiopathic non-specific interstitial pneumonia; unclassifiable idiopathic interstitial pneumonia; autoimmune interstitial lung disease [e.g., rheumatoid arthritis interstitial lung disease]; exposure-related interstitial lung disease; and mixed connective tissue disease interstitial lung disease.

8. **Idiopathic Pulmonary Fibrosis**. Approve for 3 years if the patient meets the following criteria (A, B, C, and D).
   - **65.** Patient is ≥ 40 years of age; AND
   - **66.** Forced vital capacity (FVC) is ≥ 40% of the predicted value; AND
   - **67.** The diagnosis is confirmed by one of the following (i or ii):
     - **i.** Findings on high-resolution computed tomography indicates usual interstitial pneumonia (UIP); OR
     - **ii.** A surgical lung biopsy demonstrates usual interstitial pneumonia; AND
   - **68.** Medication is prescribed by or in consultation with a pulmonologist.

9. **Interstitial Lung Disease Associated with Systemic Sclerosis.** Approve for 3 years if the patient meets the following criteria (A, B, C, and D).
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Forced vital capacity (FVC) is ≥ 40% of the predicted value; AND
   - **C)** Diagnosis is confirmed by high-resolution computed tomography.
   - **D)** Medication is prescribed by or in consultation with a pulmonologist or a rheumatologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ofev is not recommended in the following situations:

42. **Ofev is Being Used Concomitantly with Esbriet® (pirfenidone capsules)**. Esbriet is another medication indicated for IPF.[6] The effectiveness and safety of concomitant use of Ofev with Esbriet have not been established. The 2015 ATS/ERS/JRS, ALAT clinical practice guideline regarding the treatment of idiopathic pulmonary fibrosis (an update of the 2011 clinical practice guidelines) do not recommend taking Ofev and Esbriet in combination.[4] A small exploratory study was done in which patients with IPF receiving Ofev added-on Esbriet.[7] Further research is needed to determine the utility of this combination regimen. Ofev and Esbriet have not been used concomitantly in the management of systemic sclerosis-associated interstitial lung disease.

43. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual Revision	No criteria changes	12/12/2018
Early Annual Revision	The Policy header was changed to add the description "and Related Lung Disease" to the Idiopathic Pulmonary Fibrosis title. Also, the following criteria changes were made: **1. Idiopathic Pulmonary Fibrosis:** The forced vital capacity threshold was changed from ≥ 50% to ≥ 40%. Previously, only the baseline (before initiation of therapy) values were accepted but now the timing of the assessment is not specified. **2. Interstitial Lung Disease Associated with Systemic Sclerosis:** New criteria were developed based on this new Food and Drug Administration-approved use.	10/02/2019
Selected Revision	Criteria were changed as follows: **1. Chronic Fibrosing Interstitial Lung Disease:** Criteria were added to address the new indication of use. Criteria are to approve for 3 years of the patient meets all of the following: 1) The patient is ≥ 18 years of age; and 2); the forced vital capacity is ≥ 45% of the predicted value; and 3) according to the prescriber the patient has fibrosing lung disease impacting more than 10% of lung volume on high-resolution computed tomography; and 4) according to the prescriber the patient has clinical signs of progression. Notes were added that detailed clinical signs of progression and examples of conditions.	03/25/2020
Annual Revision	No criteria changes.	10/21/2020

PRIOR AUTHORIZATION POLICY

POLICY: Immune Globulin – Atgam Prior Authorization Policy

- Atgam® (lymphocyte immune globulin, anti-thymocyte globulin [equine] solution for intravenous use – Pfizer)

REVIEW DATE: 12/02/2020

OVERVIEW

Atgam, an immune globulin, is indicated for the following uses:

- **Allograft rejection**: for the management of allograft rejection in renal transplant patients. When administered with conventional therapy at the time of rejection Atgam increases the frequency of resolution of the acute rejection episode.
- **Aplastic anemia**: for the treatment of moderate to severe aplastic anemia in patients unsuitable for bone marrow transplantation. The usefulness of Atgam has not been demonstrated in patients with aplastic anemia who are suitable candidates for bone marrow transplantation or in patients with aplastic anemia secondary to neoplastic disease, storage disease, myelofibrosis, Fanconi's syndrome, or in patients known to have been exposed to myelotoxic agents or radiation.[1]

Guidelines

The use of Atgam is supported in clinical guidelines in a number of situations:[2-9]

- **Acute cellular rejection**: The Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Care of Kidney Transplant Recipients (2009), recommend anti-thymocyte globulin (ATG) as a treatment option for induction therapy, given prior to, at the time of, or immediately after transplant.[2] The KDIGO guidelines recommend ATG for the treatment of acute cellular rejection unresponsive to corticosteroids, recurrent acute cellular rejection, and for acute antibody-mediated rejection.
- **Aplastic anemia**: The British Society of Haematology guidelines for the diagnosis and management of aplastic anemia recommends immunosuppressive therapy with Atgam (equine

ATG) plus cyclosporine for the first-line treatment of non-severe aplastic anemia patients requiring treatment, severe or very severe aplastic anemia patients who lack a matched sibling donor, and severe or very severe aplastic anemia patients aged > 35 – 50 years of age.[3,4] A second course of Atgam is recommended following a relapse after the first course of therapy, or after failure to respond to the first course if the patient is ineligible for a matched unrelated donor hematopoietic stem cell transplant. In addition, Atgam is included in conditioning regimens for bone marrow transplantation.[5]

- The National Comprehensive Cancer Network (NCCN) guidelines:[6-9]
  - **Graft-vs-host disease**: The NCCN Hematopoietic Cell Transplantation Clinical Practice Guidelines (Version 2.2020 – March 23, 2020) recommend ATG as additional therapy in conjunction with corticosteroids for the management of acute steroid-refractory disease.[9]
  - **Immunotherapy-related cardiovascular toxicity**: The NCCN Guidelines for the Management of Immunotherapy-Related Toxicities (Version 1.2020 – December 16, 2019), recommend Atgam as additional treatment for severe or life-threatening myocarditis, pericarditis, arrhythmias, or impaired ventricular function, or conduction abnormalities if no improvement within 24 hours of starting pulse-dose methylprednisolone.[6,7]
  - **Myelodysplastic syndrome**: The NCCN Clinical Practice Guidelines (Version 1.2021 – September 11, 2020) recommend Atgam as a treatment option for the management of lower risk disease.[7,8] Treatment with Atgam alone or in combination with cyclosporine is recommended for select patients with clinically relevant thrombocytopenia, neutropenia, or increased marrow blasts; or for select patients with symptomatic anemia.

Other Uses With Supportive Evidence

One case report has been published which summarized the use of equine ATG for the treatment of a patient with fulminant myocarditis secondary to Opdivo® (nivolumab injection for intravenous use) therapy.[10] Equine ATG was administered according to the local protocol for acute cellular rejection and consisted of 500 mg on Day 1 and the dose was titrated by 250 mg daily to maintain a CD2/3 level of 50 – 100/µL for a total of 5 days of treatment. Resolution of ventricular arrhythmias occurred within 3 days of beginning ATG and cardiac enzymes normalized by Day 5. Cardiac biopsy 10 days after beginning ATG treatment revealed histologic improvement with significantly less myocyte necrosis.

Atgam has been utilized as a component of induction therapy for heart and lung transplantation.[11-15] In a retrospective review of 163 consecutive patients undergoing lung transplantation, 65 patients received Atgam and 98 received daclizumab as a component of induction therapy.[11] At two years after transplantation, more patients treated with Atgam had acute rejection (28% vs. 9%, respectively) and bronchiolitis obliterans (23% vs. 6.4%). In another retrospective analysis of lung transplantation in pediatric patients (n = 330), approximately half of the patients received induction therapy and 30% of these patients received horse or rabbit ATG.[12] Overall survival in the patients who received induction therapy was numerically, but not significantly longer than the patients who did not receive induction therapy (77.4 months vs. 50.8 months, respectively). Finally, an article reviewing immunosuppression in lung transplantation states that approximately 20% of the centers that utilize induction therapy use ATG (horse or rabbit).[13] In a clinical trial, patients undergoing heart transplantation were randomized to Atgam (n = 15) or daclizumab (n = 15) as a component of induction therapy.[14] There were no differences in rejection, infection, or malignancy between groups. In addition, 1 year survival was similar between groups (87% in both groups). In a prospective trial, the safety and efficacy of Atgam (n = 21) was compared with OKT3 (n = 20) in patients undergoing heart transplantation.[15] Survival at 12 months, time to first rejection episode, and rejection rate was similar between the two groups. However, viral infections (1.6 vs. 0.8) and adverse events were significantly more common with OKT3 compared with Atgam.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Atgam. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Atgam as well as the monitoring required for adverse events and long-term efficacy, approval requires Atgam to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Atgam is recommended in those who meet the following criteria:

FDA-Approved Indications

78. Allograft Rejection in Solid Organ Transplant. Approve for 1 month if the patient meets the following criteria (A and B):
- **A)** Patient meets one of the following (i or ii):
  - **i.** Atgam is used for induction therapy, prior to, at the time of, or immediately following transplantation; OR
  - **ii.** Atgam is used for the treatment of acute rejection; AND
- **B)** The medication is prescribed by or in consultation with a transplant specialist physician or a physician associated with a transplant center.

79. Aplastic Anemia. Approve for 1 month if the patient meets the following criteria (A, B, and C):
- **A)** Patient has moderate to severe disease; AND
- **B)** Patient is unsuitable for bone marrow transplantation; AND
- **C)** The medication is prescribed by or in consultation with a hematologist or a physician who specializes in the treatment of aplastic anemia.

Other Uses with Supportive Evidence

80. Allogeneic Hematopoietic Stem Cell Transplantation. Approve for 1 month if the patient meets the following criteria (A and B):
- **A)** Atgam is used as part of a conditioning regimen beginning prior to allogeneic hematopoietic stem cell transplantation; AND
- **B)** The medication is prescribed by or consultation with an oncologist or a physician who specializes in allogeneic hematopoietic stem cell transplantation.

81. Graft-Versus-Host Disease. Approve for 1 month if the patient meets the following criteria (A, B, and C):
- **A)** Patient has acute disease; AND
- **B)** Patient's disease is refractory to or resistant to corticosteroid therapy; AND
- **C)** The medication is prescribed by or consultation with an oncologist or a physician who specializes in allogeneic hematopoietic stem cell transplantation.

82. Immune Checkpoint Inhibitor-Related Toxicities. Approve for 1 month if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient has received at least one immune checkpoint inhibitor; AND
  Note: Immune checkpoint inhibitors include Opdivo® (nivolumab injection for intravenous use), Keytruda® (pembrolizumab injection for intravenous use), Tecentriq® (atezolizumab injection for intravenous use), Bavencio® (avelumab injection for intravenous use), Imfinzi® (durvalumab injection for intravenous use), Yervoy® (ipilimumab injection for intravenous use).
- **B)** Patient has life-threatening myocarditis, pericarditis, arrhythmias, or impaired ventricular function according to the prescriber; AND

C) Patient has not improved within 24 hours of starting pulse-dose methylprednisolone; AND
D) The medication is prescribed by or consultation with a cardiologist, oncologist or a physician who specializes in the treatment of immune checkpoint inhibitor-related toxicity.

83. Myelodysplastic Syndrome. Approve for 1 month if the patient meets the following criteria (A, B, and C):
A) Patient has lower risk disease; AND
Note: Lower risk disease is defined as International Prognostic Scoring System (IPSS) risk of low or intermediate-1; IPSS-Revised (IPSS-R) risk of very low, low, or intermediate; World Health Organization Prognostic Scoring System (WPSS) risk of very low, low, or intermediate.
B) Patient has one of the following according to the prescriber (i, ii, iii, or iv):
i. Clinically relevant thrombocytopenia; OR
ii. Clinically relevant neutropenia; OR
iii. Increased marrow blasts; OR
iv. Symptomatic anemia: and
C) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Atgam is not recommended in the following situations:

95. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/04/2019
Annual Revision	No criteria changes.	12/02/2020

PRIOR AUTHORIZATION POLICY

POLICY: Immune Globulin – Cytogam Prior Authorization Policy

- Cytogam® (human cytomegalovirus immune globulin intravenous liquid – Saol Therapeutics)

REVIEW DATE: 12/02/2020

OVERVIEW

Cytogam, a human cytomegalovirus (CMV) immune globulin intravenous (IGIV), is indicated for the **prophylaxis of CMV disease** associated with transplantation of kidney, lung, liver, pancreas and heart.[1]

Other Uses With Supportive Evidence

Maternal transmission of CMV to the fetus may occur at any gestation, leading to congenital CMV.[2] A study of 304 pregnant women with a primary CMV infection were offered CMV IGIV. In the therapy group, 157 women were treated with CMV IGIV low dose (100 mg/kg/infusion given once every month) or high dose (200 mg/kg/infusion given once every 2 weeks for up to 3 doses if needed). The trial demonstrated that 56% of patients without CMV IGIV vs. 30% of patients receiving CMV IGIV lead to congenital CMV infection.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cytogam. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cytogam as well as the monitoring required for adverse events and long-term efficacy, approval requires Cytogam to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cytogam is recommended in those who meet the following criteria:

FDA-Approved Indications

84. Prophylaxis of Cytomegalovirus Associated with Solid Organ Transplant. Approve for 4 months if the medication is prescribed by or in consultation with a physician affiliated with a transplant center, hematologist, or an infectious disease physician.

Other Uses with Supportive Evidence

85. Cytomegalovirus Associated with Pregnancy. Approve for 6 months if the medication is prescribed by or in consultation with an infectious disease physician or an obstetrician-gynecologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cytogam is not recommended in the following situations:

96. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/04/2019
Annual Revision	No criteria changes.	12/02/2020

PRIOR AUTHORIZATION POLICY

POLICY: Immune Globulin Intravenous Prior Authorization Policy

- Asceniv™ (immune globulin intravenous liquid-sira – ADMA Biologics)
- Bivigam® (immune globulin intravenous – AMDA Biologics, Inc.)
- Carimune® NF Nanofiltered (immune globulin intravenous – CSL Behring LLC)
- Flebogamma® DIF (immune globulin intravenous – Grifols USA LLC)
- Gammagard Liquid, Gammagard® S/D < 1 mcg/mL in 5% solution (immune globulin intravenous – Baxalta US Inc.)
- Gammaked™ (immune globulin intravenous caprylate/chromatography purified – Kedrion Biopharma)
- Gammaplex® (immune globulin intravenous – BPL Inc.)
- Gamunex®-C (immune globulin intravenous caprylate/chromatography purified – Grifols USA LLC)
- Octagam® (immune globulin intravenous – Octapharma USA Inc.)
- Panzyga® (immune globulin intravenous-ifas – Octapharma USA, Inc.)
- Privigen® Liquid (immune globulin intravenous – CSL Behring LLC)

REVIEW DATE: 08/19/2020; Selected revision 9/2/2020

OVERVIEW

Immune globulin intravenous (IVIG) products are of concentrated human immunoglobulins, primarily immunoglobulin G (IgG).

All of the US licensed products (except Octagam 10%) are FDA-approved for replacement therapy in patients with primary immune deficiencies due to defects in humoral immunity. The following indications are FDA-approved:

- **B-cell chronic lymphocytic leukemia (CLL)**, for prevention of bacterial infections in patients with hypogammaglobulinemia and/or recurrent bacterial infections.[6,18,21]
- **Chronic inflammatory demyelinating polyneuropathy (CIDP),** to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.[7,9,12]

- **Idiopathic (immune) thrombocytopenic purpura (ITP)**, acute and chronic, when a rapid rise in platelet count is needed to prevent and/or control bleeding or to allow a patient with ITP to undergo surgery.[2,4,6-9,11,12,15,23-25]
- **Kawasaki disease** in pediatric patients for the prevention of coronary artery aneurysm.[6,26]
- **Multifocal motor neuropathy (MMN)** in adults as maintenance therapy to improve muscle strength and disability.[5]
- **Primary humoral immune deficiency (PID)**, for replacement therapy, including but not limited to the humoral immune defect in the following conditions: common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA) [congenital agammaglobulinemia], Wiskott-Aldrich Syndrome, and severe combined immunodeficiencies (SCID).[1-10,12,15,16,25] Gammagard Liquid 10%, Gammaked, and Gamunex-C may be administered via intravenous (IV) or subcutaneous (SC) infusion for primary immunodeficiency.[5,7,9] IVIG is also indicated for measles prophylaxis in individuals with PID who have been exposed to measles or who are at high risk of measles exposure.[3,4,7-10,12,13,17,25,45]

IVIG are prepared from pooled plasma collected from a large number of human donors.[1-12,15,16,25] The donors in a typical pool of plasma have a wide range of antibodies against infectious agents. These products have IgG subclasses similar to that found in normal humans. Asceniv contains not only antibodies which satisfy the requirement to treat patients with primary immunodeficiencies (PID), it also has elevated levels of respiratory syncytial virus (RSV) antibodies.[19]

IVIG also is used for many off-label indications. Much of the evidence for clinical effectiveness of IVIG is anecdotal (i.e., case reports, open series, or cohort studies). Some conditions have been studied in controlled trials. Usually IVIG is indicated only if standard approaches have failed, become intolerable, or are contraindicated.

- **Antibody-mediated rejection (AMBR) in transplantation**. Current strategies for treatment of antibody-mediated rejection include plasmapheresis, intravenous immunoglobulin, and T-cell or B-cell-depleting agents.[76] Although there are no controlled trials regarding the most appropriate treatments, the benefits of immune globulin have been well described and has been used as the standard-of-care (along with plasmapheresis) in multiple studies.[18,77] Clinical practice guidelines (2009 Kidney Disease: Improving Global Outcomes) recommends a combination of corticosteroids, plasmapheresis, IVIG, and anti-CD-20 antibody and lymphocyte-depleting antibody for antibody-mediated rejection.[77,78] As in desensitization therapy, much of the information of IVIG use is in patients with kidney transplants, but the same principles apply to transplantation of other organs and tissues. Immune globulin has been used in lung transplant patients to treat ABMR[20,79,80], and a scientific statement from the American Heart Association states that primary therapy for ABMR in patients with heart transplants may include IVIG, plasmapheresis, high-dose corticosteroids, and anti-lymphocyte antibodies.[36]
- **Autoimmune mucocutaneous blistering diseases (pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid [cicatricial pemphigoid], and epidermolysis bullosa acquisita.** Conventional therapy (a systemic corticosteroid and an immunosuppressive agent) is started at the same time or before IVIG. Many case reports and uncontrolled case series suggest benefit of IVIG in patients with recalcitrant disease or in those with contraindications to conventional therapy.[28-30]
- **Cytomegalovirus (CMV) pneumonia in patients with cancer or transplant-related infection.** For CMV pneumonia, therapy consists of ganciclovir IV injection (or foscarnet IV injection if CMV is ganciclovir-resistant) and IVIG in combination. The National Comprehensive Cancer Network (NCCN) guidelines on prevention and treatment of cancer-related infections (version 2.2020 – June 5, 2020) note IVIG may be added to ganciclovir or foscarnet for treatment of CMV pneumonia.[31]
- **Dermatomyositis or polymyositis**. IVIG may be used in patients with dermatomyositis with severe active illness for whom other interventions have been unsuccessful or intolerable.[32,33] IVIG

may be considered amongst the treatment options for patients with polymyositis not responding to first line immunosuppressive treatment.[32] In uncontrolled series, IVIG has been effective in polymyositis.

- **Desensitization Therapy Prior to and Immediately after Transplantation**. Patients with preexisting anti-human leukocyte antigen (HLA) antibodies (sensitized patients) are more likely to have a positive cross match with possible donors and have a lower likelihood of receiving a transplant with longer wait times. Most of the information on use of IVIG for desensitization is in patients with kidney transplantation but many of the same principles apply to transplantation of other organs and tissues.[34,35] Current protocols include using low-dose IVIG with plasma exchange or high-dose IVIG with or without B-cell depletions with Rituxan® (rituximab injection for IV infusion).[18]
- **Guillain Barre Syndrome (GBS).** The American Academy of Neurology recommends IVIG in patients who require aid to walk within 2 or 4 weeks from the onset of neuropathic symptoms.[37] The effect of IVIG in GBS has only been investigated in randomized controlled trials in patients who are unable to walk at nadir (i.e., severely affected patients), not in mildly affected patients who are able to walk unaided at nadir.[38] IVIG is not indicated or proven to be effective in mildly affected GBS patients.[32,38]
- **Hematologic neoplasm-associated hypogammaglobulinemia or hypogammaglobulinemia after B-cell targeted therapies (secondary immunodeficiency [SID])**. Clinical guidelines for immunoglobulin use by the National Health Service- England note secondary antibody deficiency can be hypogammaglobinemia associated with therapeutic monoclonals targeted at B-cells and plasma cells, non-Hodgkin's lymphoma, CLL, multiple myeloma, or other relevant B-cell malignancies.[27]
- **Hematopoietic cell transplantation (HCT) to prevent infections**. HCT is defined as transplantation of any blood- or marrow-derived hematopoietic stem cells, regardless of transplant type (i.e., allogeneic or autologous) or cell source (i.e., bone marrow, peripheral blood, or umbilical cord blood). With regard to IVIG, guidelines recommend the following for prevention or preemptive treatment of specific infections in HCT recipients.[39] In adult or adolescent HCT recipients (allogeneic or autologous), IVIG is indicated to prevent bacterial infections in those with severe hypogammaglobulinemia (i.e., serum IgG < 400 mg/dL) during the first 100 days after HCT. In pediatric patients, IVIG is indicated in those with an allogeneic HCT if hypogammaglobulinemia is severe during the first 100 days after HCT. For prevention of bacterial infections beyond 100 days post-HCT (allogeneic or autologous), IVIG is recommended in recipients with severe hypogammaglobulinemia (i.e., serum IgG < 400 mg/dL).
- **Human Immunodeficiency Virus (HIV)-associated thrombocytopenia**. Secondary ITP can occur in patients with HIV infection.[23,24] Effective viral suppression using antiretroviral therapy improves HIV-associated cytopenias, including thrombocytopenia. Treatment of secondary ITP (HIV-associated) with short-term corticosteroid therapy increases the platelet count in a similar manner as in non-HIV infected persons and does not appear to be associated with adverse effects. The American Society of Hematology guidelines for immune thrombocytopenia recommend initial treatment with corticosteroids, IVIG, or Rh0(D) immune globulin for patients with secondary ITP due to HIV.[23,24]
- **Human Immunodeficiency Virus (HIV)-infected infants and children to prevent recurrent bacterial infections**. IVIG is no longer recommended for primary prevention of serious bacterial infections in HIV-infected children unless hypogammaglobulinemia is present or functional antibody deficiency is demonstrated by recurrent bacterial infections.[40] In children with greater than two serious bacterial infections in a 1-year period and who cannot tolerate cART, secondary

prophylaxis is indicated. The first choice of therapy for secondary prophylaxis is trimethoprim-sulfamethoxazole and IVIG every 2 to 4 weeks is an alternative. Clinicians providing care for adolescents are advised to use the US Department of Health and Human Services Adult and Adolescent HIV-guideline for the care of post-pubertal adolescents (sexual maturity rating [SMR] IV and V) and to use the pediatric guideline for guidance on the care of adolescents at SMR III or lower.[40]

- **Immunotherapy-related toxicities associated with checkpoint inhibitor therapy**. NCCN guidelines for the management of immunotherapy-related toxicities (version 1.2020 – December 16, 2020) recommend IVIG for the management of severe pneumonitis after 48 hours of methylprednisolone therapy; as treatment for severe myasthenia gravis; encephalitis; cardiovascular adverse events; inflammatory arthritis; musculoskeletal adverse events; moderate or severe Guillian-Barre Syndrome; severe transverse myelitis; bullous dermatitis; Stevens-Johnson syndrome/toxic epidermal necrolysis.[74] The American Society of Clinical Oncology also has practice guidelines on the management of immune-related adverse events in patients treated with checkpoint inhibitor therapy.[75] These practice guidelines address the above mentioned indications along with other diagnoses (e.g., severe cutaneous skin adverse reactions, myositis, autoimmune hemolytic anemia, immune thrombocytopenia).
- **Lambert-Eaton Myasthenic Syndrome (LEMS)**. LEMS is a rare presynaptic autoimmune disorder of neuromuscular transmission that is characterized by proximal muscle weakness, depressed tendon reflexes, and autonomic dysfunction.[18] Limited but moderate- to high-quality evidence from randomized controlled trials have shown that 3,4-diaminopyridine or IVIG was associated with improved muscle strength score and compounded muscle action potential amplitudes. IVIG may be used as an alternative in patients who do not respond or do not tolerate other therapies.[18]
- **Multiple myeloma**. Patients with multiple myeloma are often functionally hypogammaglobulinemic with total immunoglobulin production being elevated, but the repertoire of antibody production restricted.[31] The NCCN guidelines on multiple myeloma (version 4.2020 – May 8, 2020) recommend that IVIG should be considered in the setting of recurrent, life-threatening infections.[42]
- **Multiple sclerosis (MS), acute severe exacerbation or relapses**. Medication options for relapse management include high dose corticosteroids, intramuscular adrenocorticotrophic hormone, plasmapheresis, and IVIG. IVIG is sometimes used to treat relapses that do not respond to corticosteroids.[43] During pregnancy, relapses severe enough to require treatment can be safely managed with a short-term course of corticosteroids after the first trimester. Methylprednisolone is the preferable agent because it is metabolized before crossing the placenta.[43]
- **Multiple sclerosis (MS), post-partum to prevent relapses**. None of the disease modifying therapy for multiple sclerosis have been approved for use in women who are nursing. IVIG is the treatment of choice for post-partum mothers with MS who are nursing.[44]
- **Myasthenia Gravis**. Recommendations from an international consensus guidance statement for management of adult or juvenile myasthenia gravis include the use of IVIG in some patients.[65] Symptomatic and immunosuppressive treatment of myasthenia gravis includes pyridostigmine as initial therapy in most patients. Corticosteroids or immunosuppressive therapies are used in all patients with myasthenia gravis who have not met treatment goals after an adequate trial of pyridostigmine. A nonsteroidal immunosuppressive agent (e.g., azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus) should be used alone when corticosteroids are contraindicated or refused. In patients with refractory myasthenia gravis, chronic IVIG and chronic plasma exchange (PLEX), cyclophosphamide, or Rituxan may be used. PLEX and IVIG are

recommended as short-term treatments in patients with myasthenia gravis with life-threatening effects such as respiratory insufficiency or dysphagia; to prepare for surgery in patients with significant bulbar dysfunction; when rapid response is needed; when other treatments are not adequate; and before starting corticosteroids if necessary to prevent or minimize exacerbations. IVIG can be considered as maintenance therapy in patients with refractory myasthenia gravis or in patients with relative contraindications to immunosuppressive agents. Refractory myasthenia gravis is defined as the post intervention status is unchanged or worse after corticosteroids and at least two other immunosuppressive agents used in adequate doses for an adequate duration, with persistent symptoms or side effects that limit functioning as defined by the patient or physician.

- **Passive immunization for measles (post-exposure prophylaxis)**. When administered within 6 days of exposure, immune globulin (IG) can prevent or modify measles in patients who are nonimmune.[13] IG therapy is not indicated in persons who have received one dose of measles-containing vaccine at ≥ 12 months, unless they are severely immunocompromised. The Advisory Committee on Immunization Practices (ACIP) recommends the use of IG therapy for post-exposure prophylaxis of measles in the following patients who are at risk for severe disease and complication from measles: infants < 12 months of age; pregnant women without evidence of measles immunity; and severely immunocompromised persons.[13] For infants aged < 12 months intramuscular IG is used; infants aged 6 through 11 months can receive MMR vaccine instead of IG if given within 72 hours of exposure. IVIG is used for pregnant women and severely immunocompromised patients.
- **Passive immunization for Varicella (chickenpox) [post-exposure prophylaxis]**. HIV-infected children without a history of previous chickenpox or children who have not received two doses of varicella vaccine should receive VariZIG or, if not available, IVIG within 10 days (ideally within 4 days) after close contact with a person who has chickenpox or shingles.[41,46] VariZIG is indicated for post-exposure prophylaxis in certain patients without immunity to varicella and is given as soon as possible after exposure, preferably within 4 days, and as late as 10 days after exposure.[47] Whether to administer VariZIG depends on three factors: 1) whether the patient lacks evidence of immunity to varicella; 2) whether the exposure is likely to result in infection; and 3) whether the patient is at greater risk for varicella complications than the general population.[48] For pregnant women who cannot receive VariZIG, clinicians can choose either IVIG or closely monitor the women for signs or symptoms of varicella and institute acyclovir therapy if illness occurs.[46]
- **Pure red blood cell aplasia (PRCA) secondary to chronic (persistent) parvovirus B19 infection and immunologic subtype**. In immunosuppressed patients lacking neutralizing antibodies, IVIG has been useful for the treatment of persistent B19 infection.[49] IVIG has been used to treat severe anemia secondary to chronic B19 infection in the context of solid-organ transplantation, HIV infection, or primary antibody deficiency.[49] A Canadian expert panel of hematologists recommend prednisone followed by cyclophosphamide or cyclosporine as first-line therapy for immunologic type PRCA.[22] It considers IVIG a reasonable second-line option.
- **Stiff-Person Syndrome (Moersch-Woltman Syndrome)**. Per the European Federation of Neurological Societies, IVIG should be reserved for patients who have no symptomatic relief after the use of diazepam and/or baclofen and have severe disability in carrying out daily activities.[32]
- **Thrombocytopenia, feto-neonatal alloimmune**. Antenatal therapy with IVIG administered to the mother is effective in increasing fetal platelet counts in neonatal alloimmune thrombocytopenia.[50,51] First-line therapy for newborns with fetal/neonatal alloimmune thrombocytopenia is antigen-negative compatible platelets; IVIG is adjunctive.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of IVIG products. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with IVIG as well as the monitoring required for adverse events and long term efficacy, initial approval requires IVIG products to be prescribed by or in consultation with a physician who specialized in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of immune globulin intravenous products is recommended in those who meet the following criteria:

FDA-Approved Indications

86. Primary Immunodeficiencies (PID). Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):

i. The patient meets ONE of the following (a, b, or c):

Note: An exception can be made for the impaired antibody response if, according to the prescriber, the delay caused by pre-vaccination and post-vaccination antibody measurement would be deleterious to the patient's health.

a) The patient has a diagnosis of congenital agammaglobulinemia, X-linked agammaglobulinemia, other agammaglobulinemia due to the absence of B-cells, Wiskott-Aldrich syndrome, ataxia telangiectasia, DiGeorge syndrome, severe combined immunodeficiency (SCID), Hyper-Immunoglobulin M (IgM) syndromes, an IgG level lower than 250 mg/dL, or a primary immune deficiency which has been confirmed by genetic or molecular testing; OR

b) The patient has a diagnosis of common variable immunodeficiency (CVID), unspecified hypogammaglobulinemia, or other immunodeficiencies with significant hypogammaglobulinemia and meets the following (1 and either 2 or 3):

(1) The patient's pretreatment IgG level is below the normal range (age-adjusted and according to the normal reference range for the reporting laboratory); AND

(2) The patient has an impaired antibody response (i.e., failure to product antibodies to specific antigens); OR

(3) The patient has recurrent infections; OR

c) The patient has an IgG subclass deficiency, selective antibody deficiency (SAD), or another confirmed primary immunodeficiency and meets the following criteria (1 and 2):

(1) The patient has an impaired antibody response (i.e., failure to product antibodies to specific antigens); AND

(2) The patient has recurrent infections; AND

ii. The medication is prescribed by or in consultation with an allergist/immunologist, immunologist, otolaryngologist (ear nose and throat [ENT] physician), pulmonologist, or an infectious diseases physician who treats patients with primary immune deficiencies.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has been diagnosed with a primary immunodeficiency and is continuing to receive benefit from the product, according to the prescriber.

Note: Examples of continued benefit with the product includes increased IgG levels or prevention and/or controlling of infections.

87. B-Cell Chronic Lymphocytic Leukemia for Prevention of Bacterial Infections. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets the following criteria (i or ii, and iii):

i. The patient has an immunoglobulin G (IgG) level < 500 mg/dL (5.0 g/L); OR
ii. The patient has a history of recurrent bacterial infections; AND
iii. The medication is prescribed by or in consultation with an oncologist, hematologist, or infectious diseases physician.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient is has a positive response to therapy according to the prescriber.
Note: Examples of a positive response to therapy include maintaining an increased IgG trough level or a decrease in the number of infections.

88. Chronic Inflammatory Demyelinating Polyneuropathy or Polyradiculoneuropathy (CIDP). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following criteria (i and ii)
i. Electrodiagnostic studies support the diagnosis of CIDP; AND
ii. The medication is prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year of therapy if the patient has a clinically significant improvement in neurologic symptoms, as determined by the prescriber.
Note: Examples of improvement in neurologic symptoms include improvement in disability; nerve conduction study results improved or stabilized; physical examination show improvement in neurological symptoms, strength, and sensation. The patient may not have a full response after the initial 3 months, but there should be some response.

89. Immune Thrombocytopenia (ITP). Approve for the duration noted if the patient meets ONE of the following (A, B, C, D, or E):

Note: The diagnosis of Immune Thrombocytopenia (ITP) encompasses previous nomenclature, such as Idiopathic Thrombocytopenia, Idiopathic Thrombocytopenic Purpura, Immune Thrombocytopenic Purpura.

A) Initial Therapy – Adult ≥ 18 Years of Age. Approve for 1 year if the patient meets the following criteria (i and ii):
i. The patient meets one of the following (a, b, or c):
a) The patient has tried a systemic corticosteroid (e.g., prednisone); OR
b) There is an urgent need to increase the platelet count quickly; OR
c) A systemic corticosteroid is contraindicated according to the prescriber; AND
ii. The medication is prescribed by or in consultation with a hematologist.

B) Initial Therapy – Patient is < 18 Years of Age. Approve for 1 year if prescribed by or in consultation with a hematologist.

C) Initial Therapy – To Increase Platelet Count Before Surgical or Dental Procedures: Approve for 1 month if prescribed by or in consultation with a hematologist.

D) Initial Therapy – Pregnant Patient. Approve for 6 months if prescribed by or in consultation with a hematologist.

E) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has responded to therapy according to the prescriber.
Note: Examples of responding to therapy include increased platelet counts, absence of significant bleeding, or preventing hemorrhage/ensuring an adequate platelet count in order for delivery in pregnant patients.

90. Kawasaki Disease. Approve for 3 months if prescribed by or in consultation with a pediatric cardiologist or a pediatric infectious diseases physician.

91. Multifocal Motor Neuropathy (Treatment). Approve the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has improvement in neurologic symptoms as determined by the prescriber.
Note: Examples of improvement in neurologic symptoms include improvement in disability; grip strength improvement (measured with dynamometer); physical examination show improvement in neurological symptoms and strength.

Other Uses with Supportive Evidence

92. Antibody-Mediated Rejection (AMBR) in Transplantation. Approve for 1 year if prescribed by or in consultation with a physician affiliated with a transplant center.

93. Autoimmune Mucocutaneous Blistering Diseases (Pemphigus Vulgaris, Pemphigus Foliaceus, Bullous Pemphigoid, Mucous Membrane Pemphigoid [Cicatricial Pemphigoid], and Epidermolysis Bullosa Acquisita). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following criteria (i and ii):

i. The patient meets ONE of the following criteria (a, b, or c):

a) The patient has tried a systemic corticosteroid OR a corticosteroid is contraindicated according to the prescriber AND the patient has tried an immunosuppressive agent OR an immunosuppressive agent is contraindicated according to the prescriber; OR
Note: Examples of immunosuppressive agents include azathioprine, cyclophosphamide, dapsone, methotrexate, cyclosporine, mycophenolate mofetil, and tacrolimus.

b) The patient has rapid, debilitating, progressive disease, that cannot be controlled with a systemic corticosteroid and an immunosuppressive agent; OR

c) The disease is so serious that there is inadequate time for therapy with a systemic corticosteroid and an immunosuppressive agent to have a rapid enough effect; AND

ii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has responded to therapy according to the prescriber.
Note: Examples of response to therapy can include healing of previous lesions or fewer new lesions.

94. Cytomegalovirus (CMV) Pneumonia in Patients with Cancer or Transplant-Related Infection. Approve for 2 months if prescribed by or in consultation with an oncologist, hematologist, or an infectious diseases physician.

95. Dermatomyositis or Polymyositis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following criteria (i, ii and iii):

i. The patient has tried a systemic corticosteroid OR a corticosteroid is contraindicated according to the prescriber; AND

ii. The patient has tried an immunosuppressive agent OR an immunosuppressive agent is contraindicated according to the prescriber; AND
Note: Examples of immunosuppressive agents include azathioprine, methotrexate, cyclosporine, cyclophosphamide, and mycophenolate mofetil.

iii. The medication is prescribed by or in consultation with a neurologist or rheumatologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has responded to therapy according to the prescriber.
Note: Examples of a response to therapy includes improved muscle strength, improved neuromuscular symptoms, and improved functional ability.

96. Desensitization Therapy Prior to and Immediately after Transplantation. Approve for 1 year if prescribed by or in consultation with a physician affiliated with a transplant center.

97. Guillain Barré Syndrome (GBS). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 month (this is to provide one course of therapy [divided doses given over 2 to 5 days]) if the patient meets BOTH of the following criteria (i and ii):

i. The patient meets one of the following (a or b):

a) The medication is initiated within 2 weeks and no longer than 4 weeks of onset of neuropathic symptoms; OR
Note: Examples of neuropathic symptoms include weakness, inability to stand or walk without assistance, and respiratory or bulbar weakness.

b) The patient has had a relapse (treatment related fluctuation), but had an initial response to IVIG; AND

ii. The medication is prescribed by or in consultation with a neurologist or a specialist with experience in diagnosing and treating patients with GBS.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 month (this is to provide a second course [divided doses given over 2 to 5 days]) about 3 weeks after the first course.

98. Hematologic Neoplasm-Associated Hypogammaglobulinemia or Hypogammaglobulinemia after B-cell Targeted Therapies (Secondary Immunodeficiency [SID]). Approve for the duration noted if the patient meets ONE of the following (A or B):

Note: Some examples of B-cell targeted therapy are chimeric antigen receptor [CAR]-T cell therapy (e.g., Kymriah [tisagenlecleucel], a rituximab product, Besponsa [inotuzumab ozogamicin]).

Note: Refer to B-Bell Chronic Lymphocytic Leukemia (CLL) for Prevention of Bacterial Infections and Multiple Myeloma for diagnosis-specific criteria.

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following criteria (i, ii, and iii):

i. The patient has an immunoglobulin G (IgG) level of < 500 mg/dL (5.0 g/L) [excluding paraprotein]; AND

ii. The patient has recurrent or severe bacterial infections or there is a high risk of infection, according to the prescriber; AND

iii. The medication is being prescribed by or in consultation with an oncologist, hematologist, infectious diseases physician, or immunologist.

B) Patients Currently Receiving Immune Globulin. Approve for 6 months if the patient is having a positive response to therapy according to the prescriber.
Note: Examples of a positive response to therapy include maintaining an increased IgG trough level or a decrease in the number of infections.

99. Hematopoietic Cell Transplantation (HCT) to Prevent Bacterial Infection. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following criteria (i, ii, iii, and iv):

i. The patient has had a HCT within the previous year; AND

ii. The patient has an immunoglobulin G (IgG) level < 500 mg/dL (5.0 g/L) OR the patient has multiple myeloma or malignant macroglobulinemia; AND

iii. According to the prescriber the patient has a significant risk of having frequent and/or severe bacterial infections; AND

iv. The medication is prescribed by or in consultation with a hematologist, oncologist, or infectious diseases physician.

B) Patient is Currently Receiving Immune Globulin. Approve for 6 months if the patient is having a positive response to therapy according to the prescriber.

Note: Examples of a positive response to therapy include maintaining an increased IgG trough level, controlling the number of infections, or a decrease in the number of infections.

100. Human Immunodeficiency Virus (HIV)-Associated Thrombocytopenia. Approve for 1 month if the patient meets the following criteria (A and B):

A) The patient meets ONE of the following criteria (i or ii):

i. The patient is receiving combination antiretroviral therapy for their HIV infection; OR

ii. The patient has clinically significant bleeding complications according to the prescriber; AND

B) The medication is prescribed by or in consultation with an infectious diseases specialist or a physician who specializes in the treatment of HIV infections.

101. Human Immunodeficiency Virus (HIV)-Infected Infants and Children to Prevent Recurrent Bacterial Infections. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, and iv):

i. The patient is < 18 years of age; AND

ii. The patient is receiving combination antiretroviral therapy; AND

iii. The patient has ONE of the following (a, b, or c):

a) Hypogammaglobulinemia (i.e., IgG < 400 mg/dL [4.0 g/L]); OR

b) Functional antibody deficiency is demonstrated by poor specific antibody titers (that is, the patient does not develop specific antibody responses against protein and polysaccharide antigens); OR

c) Functional antibody deficiency is demonstrated by the patient having recurrent (two or more per year), serious bacterial infections (e.g., bacteremia, meningitis, pneumonia) despite administration of combination antiretroviral therapy and appropriate antimicrobial prophylaxis; AND

iv. The medication is prescribed by or in consultation with an infectious diseases specialist or an immunologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the frequency and/or severity of infections have decreased according to the prescriber.

102. Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy. Approve for the duration noted if the patient meets ONE of the following (A or B):

Note: Examples of checkpoint inhibitors are: Keytruda (pembrolizumab), Opdivo (nivolumab), Yervoy (ipilimumab), Tecentriq (atezolizumab), Bavencio (avelumab), Imfinzi (durvalumab).

A) Initial Therapy. Approve for 1 month if the patient meets the following criteria (i, ii, or iii):

i. The patient has tried a systemic corticosteroid and has not adequately responded to therapy; OR

Note: Examples of systemic corticosteroids include prednisone, methylprednisolone.

ii. The medication is being started with a systemic corticosteroid; OR

iii. A corticosteroid is contraindicated per the prescriber.

B) Patient is Currently Receiving Immune Globulin. Approve for 6 months if the patient is having a positive response to therapy, as determined by the prescriber, and the prescriber has determined extended therapy is required.

103. Lambert-Eaton Myasthenic Syndrome (LEMS). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 month (to allow for one course of therapy [divided doses given over 2 to 5 days]) if the patient meets the following criteria (i, ii, and iii):

i. The patient is having refractory weakness after symptomatic treatment of LEMS with an amifampridine product (e.g., Firdapse, Ruzurgi), guanidine, or pyridostigmine; AND

ii. The patient meets ONE of the following (a or b):

a) The patient has paraneoplastic LEMS; OR

b) The patient has non-paraneoplastic LEMS AND has tried a systemic corticosteroid (e.g., prednisone) or another immunosuppressive agent (e.g., azathioprine), or has a contraindication to corticosteroids and/or immunosuppressive agents, according to the prescriber; AND

iii. The medication is prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has a response or continued effectiveness, according to the prescriber.

Note: Examples of a response to therapy include improved muscle strength or other clinical response.

104. Multiple Myeloma. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following criteria (i and ii):

i. The patient has severe recurrent bacterial infections according to the prescriber; AND

ii. The medication is prescribed by or in consultation with a hematologist, oncologist, or infectious diseases specialist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year.

105. Multiple Sclerosis (MS), Acute Severe Exacerbation or Relapses. Approve for 1 month (this is to provide one course of therapy [either a single dose or in divided doses given over 1 to 5 days]) if the patient meets BOTH of the following criteria (A and B):

A) The patient meets ONE of the following criteria (i or ii):

i. The patient has either not responded to or has had a significant adverse reaction with systemic corticosteroids (e.g., methylprednisolone sodium succinate injection) OR plasma exchange; OR

Note: A trial of Acthar® H.P. gel [repository corticotropin injection; adrenocorticotropic hormone, ACTH] would also count toward meeting this requirement.

ii. A systemic corticosteroid is contraindicated according to the prescriber; AND

B) The medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of MS.

106. Multiple Sclerosis (MS), Post-Partum to Prevent Relapses. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following criteria (i and ii):

i. The patient is not currently receiving a disease modifying therapy (DMT) for MS to prevent relapses; AND

Note: Disease modifying therapy can include Avonex® (interferon beta-1a injection, IM), Plegridy® (peginterferon beta-1a SC injection), Rebif® (interferon beta-1a injection, SC), Betaseron®/Extavia® (interferon beta-1b injection), Copaxone®/Glatopa™ (glatiramer acetate

injection, SC), Gilenya® (fingolimod capsules), Lemtrada™ (alemtuzumab injection for IV use), Aubagio® (teriflunomide tablets), Mavenclad® (cladribine tablets), Mayzent® (siponimoid tablets), Tecfidera® (dimethyl fumarate capsules), Vumerity® (diroximel fumarate capsules), Zeposia® (ozanimod capsules), Tysabri® (natalizumab injection), Novantrone® (mitoxantrone injection).

ii. The medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of MS.

B) Patient is Currently Receiving Immune Globulin. Approve for a second 6 months of therapy if the patient is not taking a disease modifying therapy (DMT) for MS.

Note: Disease modifying therapy can include: Avonex (interferon beta-1a injection, IM), Plegridy (peginterferon beta-1a SC injection), Rebif (interferon beta-1a injection, SC), Betaseron/Extavia (interferon beta-1b injection), Copaxone/Glatopa (glatiramer acetate injection, SC), Gilenya (fingolimod capsules), Lemtrada (alemtuzumab injection for IV use), Aubagio (teriflunomide tablets), Mavenclad (cladribine tablets), Mayzent (siponimoid tablets), Tecfidera (dimethyl fumarate capsules), Vumerity (diroximel fumarate capsules), Zeposia (ozanimod capsules), Tysabri (natalizumab injection), Novantrone (mitoxantrone injection).

107. Myasthenia Gravis. Approve for the duration noted if the patient meets ONE of the following (A or B or C):

A) Initial Therapy for Short-Term (Acute) Use. Approve for 5 days (to allow for one course of therapy to be given in divided doses over 2 to 5 consecutive days) if the patient meets the following (i and ii):

i. The patient meets ONE of the following conditions (a, b, c, or d):

a) The patient has an exacerbation of myasthenia gravis; OR

b) The patient requires stabilization of myasthenia gravis before surgery; OR

c) The patient has been started on an immunosuppressive drug and is waiting for full effect; OR

Note: Examples of immunosuppressive drugs include azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, methotrexate, or tacrolimus.

d) The patient is starting therapy with a corticosteroid and IVIG is being given to prevent or minimize exacerbations; AND

ii. The medication is prescribed by or in consultation with a neurologist.

B) Initial Therapy for Maintenance. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, and iv):

i. The patient has refractory myasthenia gravis; AND

ii. The patient has tried pyridostigmine; AND

iii. The patient has tried immunosuppressive therapy with at least one of the following agents: azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, methotrexate, tacrolimus AND has had an inadequate response; AND

iv. The medication is prescribed by or in consultation with a neurologist.

C) Patient is Currently Receiving Immune Globulin for Maintenance Therapy. Approve for 1 year if the patient is responding according to the prescriber.

108. Passive Immunization for Measles (Post-Exposure Prophylaxis). Approve for 1 day (to allow for a single dose) if the patient meets ONE of the following criteria (A or B):

Note: For patients with primary immune deficiency, see criteria for PID.

A) The patient is pregnant and meets the following criteria (i and ii):

i. The patient has been exposed to measles and the medication will be given within 6 days of exposure; AND

ii. The patient does not have evidence of immunity to measles (i.e., the patient does not have a history of the disease or age-appropriate vaccination); OR

B) The patient meets ALL of the following criteria (i, ii, and iii):

i. The patient is severely immunocompromised; AND
Note: Examples of severe immunocompromised status include patients with bone marrow transplant, graft-versus-host disease (GVHD), acute lymphoblastic leukemia (ALL), acquired immunodeficiency syndrome (AIDS), or human immunodeficiency virus (HIV)-infected patients.

ii. The patient has been exposed to measles; AND

iii. The medication will be given within 6 days of exposure.

109. Passive Immunization for Varicella (Chickenpox) [Post-Exposure Prophylaxis]. Approve for 1 day (to allow for a single dose) if the patient meets ONE of the following criteria (A or B):

A) The patient is human immunodeficiency virus (HIV)-infected and meets ALL of the following criteria (i, ii, and iii):

i. VariZIG® (varicella zoster immune globulin [human] IM injection) is not available; AND

ii. The patient does not have evidence of immunity to varicella (i.e., patient does not have a history of the disease or age-appropriate vaccination); AND

iii. The medication is prescribed by or in consultation with an infectious diseases specialist or an immunologist; OR

B) The patient is not HIV-infected and meets ALL of the following criteria (i, ii, iii, and iv):

i. VariZIG (varicella zoster immune globulin [human] IM injection is not available; AND

ii. The patient does not have evidence of immunity to varicella (i.e., the patient does not have a history of the disease or age-appropriate vaccination); AND

iii. The patient meets ONE of the following criteria (a or b):

a) The patient is immune compromised; OR

b) The patient is pregnant; AND

iv. The medication is prescribed by or in consultation with an infectious diseases specialist or immunologist.

110. Pure Red Blood Cell Aplasia (PRCA) Secondary to Chronic (Persistent) Parvovirus B19 Infection. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 2 months if the patient meets ALL of the following criteria (i, ii and iii):

i. The patient has a chronic immunodeficiency condition; AND
Note: Examples of a chronic immunodeficiency condition include patients with HIV infection, solid organ transplants (e.g., renal, liver), chemotherapy for hematologic malignancy.

ii. The patient has clinically significant anemia as determined by the prescriber OR the patient is transfusion dependent; AND

iii. The medication is prescribed by or in consultation with an infectious diseases specialist, immunologist, hematologist, or transplant specialist.

B) Patient is Currently Receiving Immune Globulin. Approve for 3 months in patients who responded with an increase in hemoglobin to previous IVIG therapy but relapse when off IVIG or in patients who respond and require maintenance therapy to prevent relapse.

111. Pure Red Blood Cell Aplasia (PRCA), Immunologic Subtype. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 month if the patient meets ALL of the following criteria (i, ii, and iii):

i. The patient has tried a systemic corticosteroid (e.g., prednisone); AND

ii. The patient has tried either cyclophosphamide or cyclosporine; AND

iii. The medication is prescribed by or in consultation with an infectious diseases specialist, immunologist, hematologist, or transplant specialist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 month if the patient has responded with an increase in hemoglobin and reticulocytosis, according to the prescriber.

112. Stiff-Person Syndrome (Moersch-Woltman Syndrome). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following criteria (i and ii):

i. The patient meets ONE of the following criteria (a or b):

a) The patient has tried a benzodiazepine (e.g., diazepam) or baclofen; OR

b) The patient has contraindications to both a benzodiazepine AND baclofen according to the prescriber; AND

ii. The medication is prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient as responded to therapy according to the prescriber.

Note: Examples of response to therapy includes reduced stiffness or frequency of spasms, ability to walk unassisted.

113. Thrombocytopenia, Feto-neonatal Alloimmune. Approve for 6 months if the pregnant mother or newborn patient is prescribed the medication by or in consultation with a hematologist or an obstetrician.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of immune globulin intravenous is not recommended in the following situations:

97. Adrenoleukodystrophy. Evidence does not support IVIG use.[18]

98. Alzheimer's Disease (AD). In one multicenter, double-blind, Phase III, placebo-controlled trial, 390 patients with mild to moderate AD were randomized to therapy with IVIG 400 mg/kg or 200 mg/kg or to placebo given every 2 weeks for 18 months.[61] There was no statistically significant difference in the rate of cognitive decline when compared to placebo (mean 7.4 in the 400 mg/kg group; 8.9 in the 200 mg/kg group; 8.4 in the placebo group). There was not a statistically significant change in functional ability when compared to placebo (mean of -11.4 in the 400 mg/kg group; -12.4 in the 200 mg/kg group; -11.4 in the placebo group). Large placebo-controlled trials with a longer observation period are needed to established efficacy, determine the optimal dose regimen, and to confirm the safety of IVIG in the general AD poputation.[52,53]

99. Amyotrophic Lateral Sclerosis. There is insufficient evidence to recommend IVIG.[18]

100. Anemia, Aplastic. Evidence does not support IVIG use.[22]

101. Asthma. Global Initiative for Asthma (GINA) guidelines for asthma management and prevention do not include recommendations for use of IVIG.[54]

102. Atopic Dermatitis. Limited data exist to determine the utility of rituximab, omalizumab, intravenous immunoglobulin, and oral calcineurin inhibitors in the management of atopic dermatitis.[55]

103. Autism. Evidence does not support IVIG use.[18] Well-controlled, double-blind trials are needed.

104. Chronic Fatigue Syndrome. Evidence does not support IVIG use.[56] One randomized, placebo-controlled trial did not find benefits in quality of life measures nor the Profile of Mood States for IVIG.[56] Although scores were improved in IVIG and placebo treatment groups, no significance between group differences was demonstrated.

105. Complex Regional Pain Syndrome (Reflex Sympathetic Dystrophy). There is insufficient evidence to recommend IVIG. In one single center study a single dose of 0.5 g of IVIG per kg produced a decrease in pain intensity by 50% or more compared to placebo in 3 of 12 patients.[57] In a randomized, placebo-controlled, multicenter trial, low-dose immunoglobulin treatment for 6 weeks was not effective in relieving pain in patients with moderate-to-severe complex regional pain syndrome.[58] Well-controlled large-scale trials are needed.

106. Crohn's Disease. There is insufficient evidence to recommend IVIG. In one single center case collection report, 19 patients with acute Crohn's disease (Crohn's Disease Activity Index [CDAI] 284.1 ± 149.8) who were resistant to steroids received IVIG daily for 7 to 10 days.[59] Four weeks after completing therapy, 14 patients were in clinical remission (CDAI < 150). Spontaneous remissions cannot be excluded. Prospective, randomized, placebo-controlled trials are needed to determine if IVIG has a role in the treatment of Crohn's disease.

107. Cystic Fibrosis. There is insufficient evidence to recommend IVIG. In one single-center retrospective case review of 16 children with cystic fibrosis, IVIG was reportedly effective.[60] Well-designed, controlled trials are needed.[18]

108. Diabetes Mellitus, Immunotherapy. Evidence does not support IVIG use.[18,62,63] In one 2-year randomized controlled trial, IVIG was given every 2 months to children and adults with type 1 diabetes.[62] No beneficial effect was shown with IVIG compared with control and the authors concluded that IVIG therapy is unlikely to be a viable option for immunotherapy.

109. Fibromyalgia Syndrome. There is insufficient evidence to recommend IVIG. In one open-label single center study, 15 patients with fibromyalgia syndrome and distal demyelinating polyneuropathy received IVIG 400 mg/kg given daily for 5 days.[64] Pain, tenderness, and strength reportedly improved. These patients were not diagnosed with CIPD. Double-blind, placebo controlled trials are needed to determine if IVIG is effective in fibromyalgia syndrome.

110. Heart Failure, Chronic. There is insufficient evidence to recommend IVIG. In one randomized, placebo-controlled trial, IVIG given monthly for 26 weeks improved left ventricular ejection fraction (LVEF) in patients with chronic heart failure and LVEF < 40%.[66] In another controlled trial in patients with recent onset dilated cardiomyopathy and LVEF < 40%, IVIG, given for 2 consecutive days with no maintenance IVIG, did not improve LVEF more than placebo. Larger trials are needed in well-defined populations (cause and severity) to determine if IVIG has a role in the treatment of heart failure.

111. Human Immunodeficiency Virus (HIV) Infection, Adults, for Prophylaxis of Infections. IVIG is not listed in the recommendations for post exposure prophylaxis for occupational exposures to HIV; antiretroviral therapy should be used in certain circumstances after exposure to HIV infection.[67]

112. In Vitro Fertilization (IVF). There is insufficient evidence to recommend IVIG administration as part of IVF outcomes.[68]

113. Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes (POEMS) Syndrome. Evidence does not support IVIG use.[18]

114. Post-Polio Syndrome. There is insufficient evidence to recommend IVIG. Post-polio syndrome is characterized by new muscle weakness, atrophy, fatigue, and pain developing several years after the acute polio. A 2015 Cochrane Review concluded there was moderate- and low-quality evidence that IVIG has no beneficial effect of activity limitations in the short term and long term, respectively.[69] The evidence for effectiveness of IVIG on muscle strength is inconsistent.

115. Recurrent Spontaneous Pregnancy Loss (RSPL) [Including Antiphospholipid Antibody-Positive Patients]. Evidence does not support IVIG use.[70-73] In one double-blind pilot study, IVIG did not improve obstetric or neonatal outcomes beyond those achieved with a heparin and low-dose aspirin regimen.[70] In another double-blind trial (n = 82 of whom 47 had an index pregnancy) live birth rates did not differ significantly between IVIG-treated and placebo-treated women (70% vs. 63%; P =0.76; odds ratio [OR]: 1.37 [95% CI: 0.41, 4.61]).[71] The American Society for Reproductive Medicine practice committee states that several trials and meta-analyses concluded that IVIG is ineffective for primary recurrent pregnancy loss and this treatment is not recommended.[73]

116. Selective Immune Globulin A (IgA) Deficiency as the Sole Immunologic Abnormality. Evidence does not support use of IVIG.[14,18] Selective IgA deficiency is defined as a serum IgA level less than 0.07 g/L, but normal serum IgG and IgM levels in a patient greater than 4 years of age in whom other causes of hypogammaglobulinemia have been excluded.[14] Selective IgA deficiency may co-exist in some patients with poor specific IgG antibody production, with or without IgG2 subclass deficiency.[14,18] Some of these patients with a concomitant specific antibody defect might benefit from therapy with IVIG.

117. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Selected revision	**Immunodeficiency, Primary Humoral (Treatment)**: Criteria were added for patients currently receiving IVIG to approve for 1 year for the following conditions: CVID, other combined immunodeficiencies with significant hypogammaglobulinemia or antibody production defect, or unspecified hypogammaglobulinemia, if the frequency and/or severity of infections have decreased according to the prescribing physician. The conditions of XLA, SCID, Wiskott-Aldrich syndrome, and hyper-IgM syndromes are approved for 1 year. **B-Cell CLL for Prevention of Bacterial Infections**: Initial approval is for 4 months (previous duration was 1 year). For patients currently receiving IVIG, approval is for 1 year if the patient is maintaining an IgG trough (pre-dose) level of about 500 mg/dL and up to 700 mg/dL to prevent bacterial infections. **CIDP or Polyradiculoneuropathy**: Initial approval is for 3 months (previous duration was 1 year). For patients currently receiving IVIG, approval is for 1 year if the patient has a clinically significant improvement in neurologic symptoms (for example, improvement in disability; nerve conduction study results improved or stabilized; physical examination show improvement in neurological symptoms, strength, and sensation) as determined by the prescribing physician (a neurologist or in consultation with a neurologist). The patient may not have a full response after the initial 3 months, but there should be some response. **ITP or IT, Acute and Chronic**: Criteria were added for patients currently receiving IVIG to approve for 1 year in children, adolescents, and adults with persistent or chronic ITP/IT, if the patient responded with increased platelet count and/or absence of significant bleeding and the patient requires additional therapy with IVIG to prevent bleeding, according to the prescribing physician. Patients requiring additional therapy for acute bleeding, to increase platelet counts before surgical or dental procedures, pregnant patients are reviewed using the Initial Therapy criteria. **MMN (Treatment)**: Initial approval is for 6 months (previous duration was 1 year). For patients currently receiving IVIG, approval is for 1 year if the patient has improvement in neurologic symptoms as determined by the prescribing physician (a neurologist or in consultation with a neurologist). IVIG should be discontinued in patients who do not respond after the first 6 months of therapy. Approve for 1 year in patients who are responding (that is, maintaining optimal function) according to the prescribing physician. **Autoimmune Mucocutaneous Blistering Diseases (Pemphigus Vulgaris, Pemphigus Foliaceus, Bullous Pemphigoid, Mucous Membrane Pemphigoid [Cicatricial Pemphigoid], and Epidermolysis Bullosa Acquisita)**: Initial approval is for 6 months (previous duration was 1 year). For patients currently receiving IVIG, approval is for 1 year if the patient has responded (previous lesions are healing and there are fewer new lesions) according to the prescribing physician. **Dermatomyositis or Polymyositis**: Initial approval is for 6 months (previous duration was 1 year). For patients currently receiving IVIG, approval is for 1 year if the patient has responded (such as improved muscle strength, improved neuromuscular symptoms, improved functional ability) according to the prescribing physician. **Desensitization Therapy Prior to and Immediately after Solid Organ (Kidney, Heart, Lung, Liver, Intestinal) Transplantation**: Initial approval is for 4 months (previous duration was 1 year). For patients currently receiving IVIG, approval is for 1 year if given before transplantation and is for 1 dose if given post-transplantation. **Guillain Barré Syndrome**: For patients currently receiving IVIG, approval is for 1 month (to provide a second course of divided doses given over 2 to 5 days) about 3 weeks after the first course. **HCT to Prevent Bacterial Infection**: Initial approval is for 3 months (previous duration was 6 months). For patients currently receiving IVIG, approval is for 6 months if the patient requires IVIG to maintain trough IgG levels greater than 400 to 500 mg/dL AND who according to the prescribing physician have significant risk of having frequent and/or severe bacterial infections despite antibiotic therapy. **HIV-Infected Infants and Children to Prevent Recurrent Bacterial Infections**: Initial approval is for 6 months (previous duration was 1 year). For patients currently receiving IVIG, approval is for 1 year if the frequency and/or severity of infections have decreased according to the prescribing physician.	02/07/2018

	LEMS, Treatment: Initial approval is for 1 month (to allow for one course of therapy [divided doses given over 2 to 5 days]) [previous duration was 1 year]. For patients currently receiving IVIG, approval is for 1 year if the patient has a response (for example, improved muscle strength, other clinical response) or continued effectiveness, according to the prescribing physician. **Multiple Myeloma**: Initial approval is for 6 months (previous duration was 1 year). For patients currently receiving IVIG, approval is for 1 year. **MS, Acute Severe Exacerbation**: Approval is for 1 month (this is to provide one course of therapy [either a single dose or in divided doses given over 1 to 5 days]) [previous duration was 5 days]. **MS, Post-Partum to Prevent Relapses**: For patients currently receiving IVIG, approval is for a second 6 months of therapy if the patient is not taking a DMT (examples listed) for MS. Initial therapy remains at 6 months. **Myasthenia Gravis**: For patients currently receiving IVIG for maintenance therapy, approval is 1 year if the patient is responding according to the prescribing physician. Duration for short-term (acute) therapy for exacerbations or relapses remain at the same duration (one course of therapy). **PRCA Secondary to Chronic (Persistent) Parvovirus B19 Infection**: Initial approval is for 2 months (previous duration was 3 months). For patients currently receiving IVIG, approval is for 3 months in patients who responded with an increase in hemoglobin to previous IVIG therapy, but relapse when off IVIG or in patients who respond and require maintenance therapy to prevent relapse. **PRCA, Immunologic Subtype**: Initial approval is for 1 month (previous duration was 2 months). For patients currently receiving IVIG, approval is for 1 month if the patient has responded with an increase in hemoglobin and reticulocytosis, according to the prescribing physician. **Stiff-Person Syndrome (Moersch-Woltman Syndrome)**: Initial approval is for 3 months (previous duration was 1 year). For patients currently receiving IVIG, approval is for 1 year if the patient has responded (such as reduced stiffness or frequency of spasms, ability to walk unassisted) according to the prescribing physician.	
Selected revision	**Immunodeficiencies, Primary Humoral**: Age in patients with CVID or Unspecified hypogammaglobulinemia revised to be at least 2 years of age. Previously the age was at least 4 years.	03/14/2018
Annual revision	**Criteria created for the following diagnoses**: Antibody-Mediated Rejection (ABMR) in Solid Organ Transplant (e.g., Kidney, Heart, Lung, Liver), Hematologic Neoplasm-Associated Hypogammaglobulinemia (Secondary Immunodeficiency [SID]), and Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy. **B-Cell Chronic Lymphocytic Leukemia (CLL) for Prevention of Bacterial Infections**: Updated criteria to IgG level below 500 mg/dL OR a history of recurrent bacterial infections. Previously both were required. **Cytomegalovirus (CMV) Interstitial Pneumonia in Patients with Hematopoietic Cell Transplantation (HCT)** updated to Cytomegalovirus (CMV) Interstitial Pneumonia in Patients with Cancer or Transplant-Related Infection. **Removed the following conditions not recommended for approval**: Cytomegalovirus (CMV) Infection, Preemptive Therapy for CMV Infection or Treatment of CMV Disease, in Allogeneic Hematopoietic Cell (HCT) Recipients and Cytomegalovirus (CMV) Infections, Prophylaxis or Treatment in Solid Organ Transplantation. **Updated the condition not recommended for approval**: Cytomegalovirus (CMV) Disease Prophylaxis in Hematopoietic Cell Transplantation (HCT) Recipients to include Solid Organ Transplantation. **Removed specific age limit in the following diagnosis**: Passive Immunization for Varicella (Chickenpox) [Post-Exposure Prophylaxis] **Updated age to < 18 years old (previously < 13 years of age) in the following diagnosis**: Human Immunodeficiency Virus (HIV) Infected Infants and Children to Prevent Recurrent Bacterial Infections.	07/03/2020
DEU revision	Added Panzyga to the policy.	10/29/2018
Selected revision	**Immunodeficiency, Primary Humoral (Treatment)**: For the unspecified hypogammaglobulinemia diagnosis in the criterion that requires that the patient has markedly impaired antibody response to protein testing with polysaccharide antigen (pneumococcus), the option of "OR according to the prescribing physician the delay	01/16/2019

	caused by pre-vaccination and post-vaccination antibody measurement would be deleterious to the patient's health" was added.	
Annual revision	**Asceniv was added to the policy** with the same criteria as all other immune globulin products. **Immunodeficiency, Primary Humoral (Treatment) was updated to Primary Immunodeficiencies (PID)**: Criteria for PID was updated to the following: Approval if (along with prescribing by a physician specialist) the patient has a diagnosis of congenital agammaglobulinemia, X-linked agammaglobulinemia, other agammaglobulinemia due to the absence of B-cells, Wiskott-Aldrich syndrome, ataxia telangiectasia, DiGeorge syndrome, severe combined immunodeficiency (SCID), Hyper-Immunoglobulin M (IgM) syndrome, an IgG level lower than 250 mg/dL, or a primary immune deficiency which has been confirmed by genetic or molecular testing. For a diagnosis of common variable immunodeficiency (CVID), unspecified hypogammaglobulinemia, or other immunodeficiencies with significant hypogammaglobulinemia, approval if (along with prescribing physician specialist) the patients pretreatment IgG level is below the normal range AND either an impaired antibody response or recurrent infections. For a diagnosis of IgG subclass deficiency or selective antibody deficiency, approval if (along with prescribing physician specialist) the patient has an impaired antibody response and has recurrent infections. Criteria for patients currently receiving intravenous immune globulin for this diagnosis were updated to approve if the patient has been diagnosed with a primary immunodeficiency and is continuing to receive benefit from the product. **Chronic Inflammatory Demyelinating Polyneuropathy or Polyradiculoneuropathy (CIDP)**: The criterion, electrodiagnostic studies to support the diagnosis of CIDP, was added. **Hematologic Neoplasm-Associated Hypogammaglobulinemia or Hypogammaglobulinemia after B-cell Targeted Therapies (Secondary Immunodeficiency [SID])** approval condition was changed to as listed. Previously listed as Hematologic Neoplasm-Associated Hypogammaglobulinemia (Secondary Immunodeficiency [SID]). An immunologist physician was added to the list of physician specialists. **Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy**: Added the criteria or IVIG is being started with a systemic corticosteroid for Initial Therapy. **Lambert-Eaton Myasthenic Syndrome (LEMS)**: The approval condition was changed to as listed; previously, listed as "Lambert-Eaton Myasthenic Syndrome, Treatment". Criteria regarding the patient having refractory weakness after symptomatic treatment of LEMS with an amifampridine product (e.g., Firdapse, Ruzurgi), guanidine, or pyridostigmine was added. Criteria regarding non-paraneoplastic LEMS was updated to having tried a systemic corticosteroid (e.g., prednisone) or another immunosuppressive agent (e.g., azathioprine), or has a contraindication to corticosteroids and/or immunosuppressive agents, according to the prescriber. **Multiple Myeloma**: the following criteria was removed "the patient has stable (plateau phase) disease (> 3 months from diagnosis). **Multiple Sclerosis (MS), Acute Severe Exacerbation** was updated to include the wording "or relapses." Acthar HP gel was removed as one of the required alternatives. Criteria was updated as to only a corticosteroid would require to be contraindicated, according to the prescriber. **Multiple Sclerosis (MS), Post-Partum to Prevent Relapses**: Mavenclad and Mayzent were added as disease modifying therapy. **Thrombocytopenia, Fetal Alloimmune**, was updated to include not only the pregnant patient, but the newborn as well. Criteria that the patient is pregnant and receiving antenatal therapy was removed. **Wording in each applicable criteria** that referenced "determined by the prescribing physician" was changed to "determined by the prescriber." **Conditions Not Recommended for Approval**: The following were removed from the list: Cytomegalovirus Disease Prophylaxis in Hematopoietic Cell Transplantation Recipients or in Solid Organ Transplantation; Epilepsy, Pediatric Intractable; Graft Versus Host Disease, Acute (Within First 100 days After Hematopoietic Cell Transplantation); Graft Versus Host Disease, Chronic, Prevention in Hematopoietic Cell Transplantation (HCT) Recipient; Hematopoietic Cell Transplantation in	7/31/2019

	Allogeneic Recipients from Human Leukocyte Antigen Identical Sibling Donors; Immune Globulin M Paraprotenicemic Demyelinating Neuropathy (or Other Paraproteinemic Demyelinating Neuropathies); Infantile Spasms (West Syndrome); Marburg Variant Multiple Sclerosis; Multiple Sclerosis, Primary Progressive; Multiple Sclerosis, Secondary Progressive; Multiple Sclerosis, Relapsing Remitting for the Prevention of Relapses; Nephropathy, Membranous; Systemic Lupus Erythematosus; Systemic Sclerosis (Scleroderma); and Thrombocytopenia, Heparin-Induced. **Polyneuropathy** was added to the Condition of Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes (POEMS Syndrome).	
Annual revision	**Primary Immunodeficiencies (PID)**: In Initial Therapy, the wording of "or another confirmed primary immunodeficiency" was added. For Continuation Therapy, the examples of benefits from the product were moved to a Note and the wording "according to the prescriber" was added. **B-Cell Chronic Lymphocytic Leukemia for Prevention of Bacterial Infections**: Added "having a positive response to therapy according to the prescriber" and placed current examples of a positive response as a note. **Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) or Polyradiculoneuropathy**: For Continuation Therapy, moved examples of a clinically significant improvement to a note. Removed a neurologist or in consultation with a neurologist for continuation criteria. **Idiopathic (Immune) Thrombocytopenic Purpura (ITP) or Immune Thrombocytopenia [IT] Acute and Chronic** was updated to Immune Thrombocytopenia (ITP). The following note was added: The diagnosis of Immune Thrombocytopenia (ITP) encompasses previous nomenclature, such as Idiopathic Thrombocytopenia, Idiopathic Thrombocytopenic Purpura, Immune Thrombocytopenic Purpura. In Initial Therapy for adults ≥ 18 years of age (previously > 17 years of age), criteria were updated to require the patient try a systemic corticosteroid, or there is an urgent need to increase platelet count quickly, or to allow if a systemic corticosteroid is contraindicated according to the prescriber. Previous criteria that separated out adults and children with acute bleeding and those with persistent or chronic disease were removed. Previous criteria of specifying platelet counts for adults with acute bleeding, persistent or chronic disease, and to increase platelet counts prior to surgery were removed. The requirement for adults that a corticosteroid be started with immune globulin if there is an urgent need to increase the platelet count quickly was removed. In Initial Therapy for children and adolescents (< 18 years of age) [previously ≤ 17 years of age], to increase platelet counts before surgical procedures, and pregnant patients, the criteria were updated to only include a requirement for the prescriber's specialty. Previous criteria that addressed children and adolescents with inaccessibility issues, activity level, and noncompliance were removed. The specific wording regarding pregnant patients, including "before normal vaginal delivery, cesarean section, or spinal or epidural anesthesia" and "pregnant patient in any trimester" was removed and replaced with the general term of "pregnant patients". The duration of approval was updated from 2 weeks and 3 months, per the respective classifications, to 6 months for any pregnant patient. For Continuation Therapy, a requirement was added that the patient has responded to therapy according to the prescriber; and the examples of responding to therapy were moved to a Note. **Kawasaki Disease**: The criteria were updated from approval of a single dose to an approval duration of 3 months. The criterion that the patient had signs and symptoms required for a second dose of immune globulin was removed since the intent of the criteria assumed the patient was given a first dose of the product in the hospital. **Multifocal Motor Neuropathy (MMN)**. For Continuation Therapy, moved examples of a clinically significant improvement to a note. Removed a neurologist or in consultation with a neurologist for continuation criteria. **Antibody-Mediated Rejection (ABMR) in Solid Organ Transplantation (e.g., Kidney, Heart, Lung, Liver)** was updated to Antibody-Mediated Rejection (ABMR) in Transplantation. **Autoimmune Mucocutaneous Blistering Diseases**. In the initial therapy criteria, examples of immunosuppressive agents were updated to notes. In the continuation criteria, examples of response to therapy were updated to notes.	08/19/2020

	Cytomegalovirus (CMV) Interstitial Pneumonia in Patients with Cancer or Transplant-Related Infection was updated to Cytomegalovirus (CMV) Pneumonia in Patients with Cancer or Transplant-Related Infection. **Dermatomyositis or Polymyositis**. In the initial therapy criteria, examples of immunosuppressive agents were updated to notes. In the continuation criteria, examples of response to therapy were updated to notes. **Desensitization Therapy Prior to and Immediately after Solid Organ (Kidney, Heart, Lung, Liver, Intestinal) Transplantation** was updated to Desensitization Therapy Prior to and Immediately after Transplantation. In Continuation Therapy, the criterion regarding the timing of administration was removed. Criteria was updated to approve for 1 year if the product is prescribed by or in consultation with a physician affiliated with a transplant center. **Guillain Barre Syndrome (GBS)**. Neuropathic symptoms were moved from criterion to a note. **Hematologic Neoplasm-Associated Hypogammaglobulinemia or Hypogammaglobulinemia after B-cell Targeted Therapies (Secondary Immunodeficieny [SID])**. Added IgG level in units of g/L. Continuation criteria: updated wording to having a positive response to therapy according to the prescriber and moved examples of a positive response to a note. **Hematopoietic Cell Transplantation (HCT) to Prevent Bacterial Infection**. Added IgG level in units of g/L. Continuation criteria: updated wording to having a positive response to therapy according to the prescriber and moved examples of a positive response to a note. **Human Immunodeficiency Virus (HIV)-Infected Infants and Children to Prevent Recurrent Bacterial Infections**. Added IgG level in units of g/L. **Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy**. Initial therapy criteria- moved examples of systemic corticosteroid therapy to a note. **Lambert-Eaton Myasthenic Syndrome (LEMS)**. Continuation criteria- moved examples of a response to therapy to a note. **Myasthenia Gravis**. Moved examples of immunosuppressive drugs to notes. **Passive Immunization for Measles (Post-Exposure Prophylaxis).** Moved examples of severe immunocompromised status into a note. **Pure Red Blood Cell Aplasia (PRCA) Secondary to Chronic [Persistent] Parvovirus B19**. Moved examples of chronic immunodeficiency conditions to a note. **Stiff-Person Syndrome (Moersch-Woltman Syndrome)**. Continuation therapy – moved examples of response to therapy to a note.	
Selected Revision	From continuation criteria, removed the wording "intravenous."	09/02/2020

PRIOR AUTHORIZATION POLICY

POLICY: Immune Globulin Subcutaneous Prior Authorization Policy

- Cutaquig® (immune globulin subcutaneous 16.5% solution – Octapharma USA, Inc.)
- Cuvitru™ (immune globulin subcutaneous 20% solution – Baxalta US Inc.)
- Gammagard Liquid (immune globulin infusion 10% solution – Baxalta US Inc.)
- Gammaked™ (immune globulin injection 10% caprylate/chromatography purified – Kedrion Biopharma, Inc.)
- Gamunex®-C (immune globulin injection 10% caprylate/chromatography purified – Grifols)
- Hizentra® (immune globulin subcutaneous 20% liquid – CSL Behring LLC)
- HyQvia (immune globulin infusion 10% with recombinant human hyaluronidase – Baxalta US Inc.)
- Xembify® (immune globulin subcutaneous 20% solution – Grifols Therapeutics LLC)

REVIEW DATE: 08/19/2020; Selected revision 09/02/2020

OVERVIEW

Immune globulin subcutaneous (SCIG) products are concentrated human immunoglobulins, primarily immunoglobulin G (IgG), that are prepared from pooled plasma collected from a large number of human donors. SCIG products are indicated for the following uses:

- **Chronic inflammatory demyelinating polyneuropathy**, for maintenance therapy in adults.[4]
- **Primary humoral immune deficiency (PID),** for replacement therapy, including but is not limited to the humoral defect in the following conditions: common variable immunodeficiency, X-linked agammaglobulinemia (congenital agammaglobulinemia), Wiskott-Aldrich syndrome, and severe combined immunodeficiencies (SCID).[1-5,7-9] SCIG is also indicated for measles prophylaxis in individuals with PID who have been exposed to measles or who are at high risk of measles exposure.[2-4,6,9]

Hizentra, Cuvitru, Xembify, and Cutaquig are indicated as a subcutaneous (SC) infusion only.[4,7-9] Gammagard Liquid, Gammaked, and Gamunex-C may be administered as a SC infusion or an intravenous infusion for PID.[1-3] HyQvia is indicated for SC infusion only, with sequential infusion of the recombinant human hyaluronidase first and followed 10 minutes later with the immune globulin infusion.[5] The recombinant human hyaluronidase acts locally to increase dispersion and absorption of the immune globulin. HyQvia has a Limitation of Use that the safety and efficacy of chronic use of recombinant human hyaluronidase in HyQvia have not been established in conditions other than PID. The safety of HyQvia has also not been established in children.[5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of SCIG products. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with SCIG as well as the monitoring required for adverse events and long-term efficacy, initial approval requires SCIG products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Cutaquig, Cuvitru, Gammagard Liquid, Gammaked, Gamunex-C, Hizentra, and Xembify (all listed products except HyQvia) is recommended in those who meet the following criteria:

FDA-Approved Indications

114. Primary Immunodeficiencies (PID). Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 1 year if the patient meets BOTH of the following criteria (i and ii):

i. The patient meets ONE of the following (a, b, or c):

Note: An exception can be made for the impaired antibody response if, according to the prescriber, the delay caused by pre-vaccination and post-vaccination antibody measurement would be deleterious to the patient's health.

a) The patient has a diagnosis of congenital agammaglobulinemia, X-linked agammaglobulinemia, other agammaglobulinemia due to the absence of B-cells, Wiskott-Aldrich syndrome, ataxia telangiectasia, DiGeorge syndrome, severe combined immunodeficiency (SCID), Hyper-Immunoglobulin M (IgM) syndromes, an IgG level lower than 250 mg/dL, or a primary immune deficiency which has been confirmed by genetic or molecular testing; OR

b) The patient has a diagnosis of common variable immunodeficiency (CVID), unspecified hypogammaglobulinemia, or other immunodeficiencies with significant hypogammaglobulinemia and meets the following (1 and either 2 or 3):

(1) The patient's pretreatment IgG level is below the normal range (age-adjusted and according to the normal reference range for the reporting laboratory); AND
(2) The patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens); OR
(3) The patient has recurrent infections; OR

c) The patient has an IgG subclass deficiency, selective antibody deficiency (SAD), or another confirmed primary immunodeficiency and meets the following (1 and 2):
(1) The patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens); AND
(2) The patient has recurrent infections; AND

ii. The medication is prescribed by or in consultation with an allergist/immunologist, immunologist, otolaryngologist (ear nose and throat [ENT] physician), pulmonologist, or an infectious diseases physician who treats patients with primary immune deficiencies.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has been diagnosed with a primary immunodeficiency and, according to the prescriber, the patient is continuing to receive benefit from the product.
Note: Examples of receiving benefit from the product would include increased IgG levels, preventing or controlling infections.

115. Chronic Inflammatory Demyelinating Polyneuropathy or Polyradiculoneuropathy (CIDP). Approve for the duration noted if the patient meets ONE the following criteria (A or B):

A) Initial Therapy. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
i. The patient is ≥ 18 years of age; AND
ii. Electrodiagnostic studies support the diagnosis of CIDP; AND
iii. The medication has been prescribed by or in consultation with a neurologist; AND

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has a clinically significant improvement in neurologic symptoms, as determined by the prescriber.
Note: Examples of improvement in neurologic symptoms include improvement in disability; nerve conduction study results improved or stabilized; physical examination show improvement in neurological symptoms, strength, and sensation.

II. Coverage of HyQvia is recommended in those who meet the following criteria:

FDA-Approved Indications

1. Primary Immunodeficiencies (PID). Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 1 year if the patient meets ALL of the following criteria (i, ii and iii):
i. The patient is ≥ 18 years of age; AND
ii. The patient meets ONE of the following (a, b, or c):
Note: An exception can be made for the impaired antibody response if, according to the prescriber, the delay caused by pre-vaccination and post-vaccination antibody measurement would be deleterious to the patient's health.

a) The patient has a diagnosis of congenital agammaglobulinemia, X-linked agammaglobulinemia, other agammaglobulinemia due to the absence of B-cells, Wiskott-Aldrich syndrome, ataxia telangiectasia, DiGeorge syndrome, severe combined immunodeficiency (SCID), Hyper-Immunoglobulin M (IgM) syndromes, an IgG level lower than 250 mg/dL, or a primary immune deficiency which has been confirmed by genetic or molecular testing; OR

b) The patient has a diagnosis of common variable immunodeficiency (CVID), unspecified hypogammaglobulinemia, or other immunodeficiencies with significant hypogammaglobulinemia and meets the following (1 and either 2 or 3):

(1) The patient's pretreatment IgG level is below the normal range (age-adjusted and according to the normal reference range for the reporting laboratory); AND
(2) The patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens); OR
(3) The patient has recurrent infections; OR

c) The patient has an IgG subclass deficiency, selective antibody deficiency (SAD), or another confirmed primary immunodeficiency and meets the following (1 and 2):
(1) The patient has an impaired antibody response (i.e., failure to produce antibodies to specific antigens); AND
(2) The patient has recurrent infections; AND

iii. The medication is prescribed by or in consultation with an allergist/immunologist, immunologist, otolaryngologist (ear nose and throat [ENT] physician), pulmonologist, or an infectious diseases physician who treats patients with primary immune deficiencies.

B) Patient is Currently Receiving Immune Globulin. Approve for 1 year if the patient has been diagnosed with a primary immunodeficiency and, according to the prescriber, the patient is continuing to receive benefit from the product.
Note: Example of receiving benefit from the product would include increased IgG levels, preventing or controlling infections.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of SCIG is not recommended in the following situations:

118. Selective Immune Globulin A (IgA) Deficiency as the Sole Immunologic Abnormality. Selective IgA deficiency is defined as a serum IgA level less than 0.07 g/L, but normal serum IgG and IgM levels in a patient > 4 years of age in whom other causes of hypogammaglobulinemia have been excluded.[11] Selective IgA deficiency may co-exist in some patients with poor specific IgG antibody production, with or without IgG2 subclass deficiency.[10,11] Some of these patients with a concomitant specific antibody defect may benefit from therapy with SCIG.

119. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	Added criteria for the diagnosis chronic inflammatory demyelinating polyneuropathy (CIDP).	07/11/2018
Selected revision	Cutaquig was added to the policy with the same criteria that applies to the other products with the exception of HyQvia. **Immunodeficiency, Primary Humoral (Treatment)**: For the unspecified hypogammaglobulinemia diagnosis in the criterion that requires that the patient has markedly impaired antibody response to protein testing with polysaccharide antigen (pneumococcus), the option of "OR according to the prescribing physician the delay caused by pre-vaccination and post-vaccination antibody measurement would be deleterious to the patient's health" was added.	01/16/2019
Annual Revision	Xembify was added to the policy with the same criteria that applies to the other products with the exception of HyQvia. **Immunodeficiency, Primary Humoral (Treatment) was updated to Primary Immunodeficiencies (PID)**: Criteria for PID was updated to the following: Approval if (along with prescribing by a physician specialist) the patient has a diagnosis of congenital agammaglobulinemia, X-linked agammaglobulinemia, other agammaglobulinemia due to the absence of B-cells, Wiskott-Aldrich syndrome, ataxia telangiectasia, DiGeorge syndrome, severe combined immunodeficiency (SCID), Hyper-Immunoglobulin M (IgM) syndrome, an IgG level lower than 250 mg/dL, or a primary immune deficiency which has been confirmed by genetic or molecular testing. For a diagnosis of common variable immunodeficiency (CVID), unspecified hypogammaglobulinemia, or other immunodeficiencies with significant hypogammaglobulinemia, approval if (along with prescribing physician specialist) the patients pretreatment IgG level is below the normal range AND either an impaired antibody response or recurrent infections. For a diagnosis of IgG subclass deficiency or selective antibody deficiency, approval if (along with prescribing physician specialist) the patient has an impaired antibody response and has recurrent infections. Criteria for patients currently receiving subcutaneous immune globulin for this diagnosis were updated to approve if the patient has been diagnosed with a primary immunodeficiency and is continuing to receive benefit from the product. **Chronic Inflammatory Demyelinating Polyneuropathy or Polyradiculoneuropathy (CIDP)**: the criterion, electrodiagnostic studies to support the diagnosis of CIDP, was added. Wording in reference to "determined by the prescribing physician" was changed to "determined by the prescriber."	07/31/2019
Annual Revision	**Primary Immunodeficiencies (PID)**: In Initial Therapy, the wording of "or another confirmed primary immunodeficiency" was added. For Continuation Therapy, the examples of benefits from the product were moved to a Note and the wording "according to the prescriber" was added. **Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) or Polyradiculoneuropathy**: For Continuation Therapy, moved examples of a clinically significant improvement to a note. Removed a neurologist or in consultation with a neurologist for continuation criteria. **Removed the following condition not recommended for approval**: HyQvia in Patients < 18 years of Age. Age is already addressed in the HyQvia criteria.	08/19/2020
Selected Revision	For continuation criteria, removed the wording "subcutaneous."	09/02/2020

PRIOR AUTHORIZATION POLICY

POLICY: Immunologicals – Cinqair Prior Authorization Policy

- Cinqair® (reslizumab injection for intravenous use – Teva Respiratory)

REVIEW DATE: 02/17/2021

OVERVIEW

Cinqair, an interleukin-5 antagonist monoclonal antibody, is indicated for **severe asthma** as add-on maintenance treatment of patients ≥ 18 years of age who have an eosinophilic phenotype.[1] Limitations of Use: Cinqair is not indicated for the treatment of other eosinophilic conditions or for the relief of acute bronchospasm/status asthmaticus.

Clinical Efficacy

The Cinqair pivotal studies included adult and adolescent patients with moderate to severe asthma.[2-4] In general, patients were required to have baseline blood eosinophil levels ≥ 400 cells/microliter despite therapy with a medium to high dose inhaled corticosteroid (ICS) with or without a second controller medication (two of the studies).[2-4] In one study that did not require patients to have elevated eosinophils at baseline, clinical benefit in regard to forced expiratory volume in 1 second (FEV_1) was not statistically significant with Cinqair vs. placebo. However, a significant improvement was observed in a subgroup of patients with baseline eosinophil levels ≥ 400 cells/microliter.

Guidelines

The Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention (2020) proposes a step-wise approach to asthma treatment.[5] Cinqair is listed as an option for add-on therapy in patients ≥ 18 years of age with difficult-to-treat, severe eosinophilic asthma (i.e., asthma that cannot be managed by therapy with an ICS/long-acting $beta_2$-agonist [LABA] combination with or without an additional controller). Higher blood eosinophil levels, more exacerbations in the previous year, adult-onset asthma, nasal polyposis, and maintenance oral corticosteroids at baseline may predict a good asthma response to Cinqair.

According to the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (2014; updated in 2020), severe asthma is defined as asthma which requires treatment with a high-dose ICS in addition to a second controller medication (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or asthma which remains uncontrolled despite this therapy.[6,7] Uncontrolled asthma is defined as asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids or asthma that meets one of the following four criteria:

1) Poor symptom control: Asthma Control Questionnaire consistently ≥ 1.5 or Asthma Control Test < 20;
2) Frequent severe exacerbations: two or more bursts of systemic corticosteroids in the previous year;
3) Serious exacerbations: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year;
4) Airflow limitation: FEV_1 < 80% predicted after appropriate bronchodilator withholding.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cinqair. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cinqair as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Cinqair to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cinqair is recommended in those who meet the following criteria:

FDA-Approved Indications

10. Asthma. Approve Cinqair for the duration noted if the patient meets one of the following conditions (A or B):

69. Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv, and v):

- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient has a blood eosinophil count ≥ 400 cells per microliter within the previous 4 weeks or within 4 weeks prior to treatment with any anti-interleukin-5 therapy; AND
  Note: Examples of anti-interleukin-5 therapies include Cinqair, Fasenra® (benralizumab injection for subcutaneous use), and Nucala® (mepolizumab injection for subcutaneous use).
- **iii.** Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a and b):
  - **a)** An inhaled corticosteroid; AND
  - **b)** At least one additional asthma controller or asthma maintenance medication; AND

  Note: Examples of additional asthma controller or asthma maintenance medications are inhaled long-acting beta$_2$-agonists, inhaled long-acting muscarinic antagonists, leukotriene receptor antagonists, anti-interleukin-5 therapies (e.g., Cinqair, Fasenra, Nucala), and theophylline. Use of a combination inhaler containing both an inhaled corticosteroid and a long-acting beta$_2$-agonist would fulfil the requirement for both criteria a and b.
- **iv.** Patient has asthma that is uncontrolled or was uncontrolled at baseline as defined by ONE of the following (a, b, c, d, or e):
  - **a)** Patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR
  - **b)** Patient experienced one or more asthma exacerbation(s) requiring hospitalization or an Emergency Department visit in the previous year; OR
  - **c)** Patient has a forced expiratory volume in 1 second (FEV_1) < 80% predicted; OR
  - **d)** Patient has an FEV_1/forced vital capacity (FVC) < 0.80; OR
  - **e)** Patient has asthma that worsens upon tapering of oral corticosteroid therapy; AND

  Note: "Baseline" is defined as prior to receiving any Cinqair or other anti-interleukin-5 therapies (i.e., Fasenra or Nucala).
- **v.** The medication is prescribed by or in consultation with an allergist, immunologist, or pulmonologist.

70. Patient is Currently Receiving Cinqair. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):

- **i.** Patient has already received at least 6 months of therapy with Cinqair; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy with Cinqair should be considered under criterion 1A (Asthma, Initial Therapy).

ii. Patient continues to receive therapy with one inhaled corticosteroid or one inhaled corticosteroid-containing combination inhaler; AND

iii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Cinqair therapy are decreased asthma exacerbations; decreased asthma symptoms; decreased hospitalizations, emergency department/urgent care, or medical clinic visits due to asthma; and decreased requirement for oral corticosteroid therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cinqair is not recommended in the following situations:

44. Concurrent use of Cinqair with Another Anti-Interleukin Monoclonal Antibody. The efficacy and safety of Cinqair used in combination other anti-interleukin monoclonal antibodies (e.g., Nucala® [mepolizumab injection for subcutaneous use], Fasenra® [benralizumab subcutaneous injection], Dupixent® [dupilumab subcutaneous injection]) have not been established.

45. Concurrent use of Cinqair with Xolair® (omalizumab injection for subcutaneous use). Xolair is a recombinant humanized immunoglobulin G (IgG)1κ monoclonal antibody indicated for use in patients ≥ 6 years of age with moderate to severe persistent asthma and who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICSs.[8] Xolair is also indicated for chronic idiopathic urticaria in adults and adolescents 12 years of age and older who remain symptomatic despite H_1 antihistamine treatment and for nasal polyps, as add-on maintenance treatment in patients ≥ 18 years of age with an inadequate response to nasal corticosteroids. The efficacy and safety of Cinqair in combination with Xolair have not been established.

46. Eosinophilic Esophagitis, or Eosinophilic Gastroenteritis. Cinqair is not indicated for the treatment of eosinophilic conditions other than asthma.[1] In addition to a small pilot study, one randomized, double-blind, placebo controlled study (n =226) evaluated the efficacy of Cinqair in pediatric and adolescent patients with eosinophilic esophagitis.[9,10] In this study, patients were randomly assigned to receive Cinqair IV at varying doses for 12 weeks. At Week 15, peak esophageal eosinophil counts were reduced from baseline and all reductions with Cinqair were significant compared with placebo. Improvements in physician's global assessment scores were also observed in all groups (including placebo), but the difference between Cinqair and placebo was not statistically significant. Guidelines for the management of eosinophilic esophagitis from the American Gastroenterological Association (AGA) and the Joint Task Force on Allergy-Immunology Practice Parameters (2020) only recommend using anti-interleukin-5 therapies in the context of a clinical trial.[11] Additional, well-controlled trials are needed to determine the role of Cinqair in the treatment of eosinophilic esophagitis and eosinophilic gastroenteritis.

47. Hypereosinophilic Syndrome. Cinqair is not indicated for the treatment of eosinophilic conditions other than asthma.[1] One very small pilot study (n = 4) evaluated the safety and efficacy of Cinqair in patients with hypereosinophilic syndrome who were refractory to or intolerant of treatment with conventional therapy.[12] A single dose of Cinqair resulted in a response in two of four patients. In the two responders, blood eosinophil counts dropped to within the normal range within 48 hours of the Cinqair infusion and this was accompanied by an improvement in clinical signs and symptoms. The 2019 World Health Organization (WHO)-defined eosinophilic disorders update on diagnosis, risk stratification, and management notes that Cinqair has not been evaluated extensively for the treatment of hypereosinophilic syndrome; use of anti-interleukin-5 approaches for the treatment of hypereosinophilic syndrome remains investigational.[13] Corticosteroids are the cornerstone of therapy

for several forms of hypereosinophilic syndrome. In patients who have idiopathic hypereosinophilic syndrome and end organ damage, enrollment into an anti-interleukin-5/anti-interleukin-5 receptor antibody clinical trial is recommended as second-line therapy. Similarly, in patients with lymphocyte-variant hypereosinophilic syndrome, enrollment into an anti-interleukin-5/anti-interleukin-5 receptor antibody clinical trial is also recommended as second-line therapy. Additional, well-controlled trials are needed to determine the role of Cinqair in the treatment of hypereosinophilic syndrome.

48. Nasal Polyps. Cinqair is not indicated for the treatment of nasal polyps.[1] One double-blind, placebo-controlled, randomized safety and pharmacokinetic study (n = 24) evaluated the use of Cinqair in patients with nasal polyps.[14] Patients received a single infusion of either Cinqair 3 mg/kg, Cinqair 1 mg/kg, or placebo. It was reported that blood eosinophil counts and concentrations of eosinophil cation protein were reduced for up to 8 weeks following the Cinqair infusion. Nasal polyp scores improved for approximately 4 weeks in one-half of patients receiving active treatment. Additionally, a pooled subgroup analysis from the two pivotal Cinqair asthma exacerbation trials found that in patients with inadequately controlled asthma and chronic sinusitis with nasal polyps (n = 150) Cinqair demonstrated enhanced efficacy. Patients in this subgroup experienced an 83% reduction the clinical asthma exacerbation rate with Cinqair vs. placebo.[15] The magnitude of this reduction was greater than that observed with the overall study population. A 2014 Practice Parameter on the Diagnosis and Management of Rhinosinusitis and a 2020 Practice Parameter for the Management of Rhinitis from the from the Joint Task Force on Practice Parameters (JTFPP), representing the American Academy of Allergy, Asthma, & Immunology (AAAAI); the American College of Allergy, Asthma, & Immunology (ACAAI); and the Joint Council of Allergy, Asthma, & Immunology note that Cinqair has shown benefit in the treatment of patients with chronic rhinosinusitis with nasal polyps.[16-19] However, it is noted that Cinqair is not approved for this use. A 2015 Clinical Practice Guideline update on Adult Sinusitis from the American Academy of Otolaryngology (AAO) address the management of nasal polyps, but do not address Cinqair[20] Additional, well-designed, controlled trials are needed to determine the role of Cinqair in the treatment of patients with nasal polyps who do not have asthma.

49. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	Updated initial therapy criteria for "Asthma in Patients with Severe Disease and an Eosinophilic Phenotype" to more concisely state the previous therapies required. Added the following note: An exception to the requirement for a trial of one additional asthma controller/maintenance medication (criterion b) can be made if the patient has already received anti-IL-5 therapy (e.g., Cinqair, Fasenra, Nucala) used concomitantly with an ICS for at least 3 consecutive months.	01/23/2019
Selected Revision	**Asthma**: Approval indication was changed from "Asthma in Patients with Severe Disease and an Eosinophilic Phenotype" to "Asthma". Wording in reference to "according to the prescribing physician" was changed to "according to the prescriber". Added Wixela Inhub, a generic to Advair Diskus, to list of examples of asthma controller/maintenance medications.	10/23/2019
Annual Revision	• **Asthma**: Removed lists of examples of inhaled asthma controller/maintenance medications. • **Hypereosinophilic Syndrome**: Condition not recommended for approval was changed from "Hypereosinophilic Syndrome, Idiopathic" to "Hypereosinophilic Syndrome".	02/12/2020
Annual Revision	No criteria changes.	02/17/2021

IL – Interleukin; ICS – Inhaled corticosteroids.

PRIOR AUTHORIZATION POLICY

POLICY: Immunologicals – Dupixent Prior Authorization Policy

- Dupixent® (dupilumab subcutaneous injection – Regeneron/sanofi-aventis)

REVIEW DATE: 02/17/2021

OVERVIEW

Dupixent, an interleukin-4 receptor alpha (IL-4Rα) antagonist, is indicated for the following uses:[1]

- **Asthma,** as an add-on maintenance treatment in patients ≥ 12 years of age with moderate-to-severe disease with an eosinophilic phenotype or with oral corticosteroid dependent asthma. Limitation of Use: Dupixent is not indicated for the relief of acute bronchospasm or status asthmaticus.

- **Atopic dermatitis,** for the treatment of patients ≥ 6 years of age with moderate to severe disease whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.
- **Chronic rhinosinusitis with nasal polyposis (CRSwNP),** as an add-on maintenance treatment in adult patients with inadequately controlled disease.

Clinical Efficacy

Asthma

Two Dupixent pivotal studies included patients ≥ 12 years of age who had moderate to severe persistent asthma that was uncontrolled despite treatment with a medium- to high-dose inhaled corticosteroid (ICS) and up to two additional controller medications.[2,4] Dupixent significantly reduced the annual exacerbation rate compared with placebo, but higher baseline eosinophil levels were correlated with larger asthma exacerbation reductions and greater increases in lung function parameters than were observed in patients with lower baseline blood eosinophil levels (i.e., < 150 cells/microliter). In a third study, oral corticosteroid-dependent patients with severe asthma were able to significantly reduce their oral corticosteroid doses and had reduced exacerbations with Dupixent compared with placebo.[3]

Atopic Dermatitis

The three pivotal Dupixent studies enrolled adults with moderate to severe chronic atopic dermatitis.[1,5,6] Patients had atopic dermatitis that affected ≥ 10% of their body surface area (BSA) and had a recent history of an inadequate response to a sufficient course of topical therapy (e.g., corticosteroids and/or calcineurin inhibitors). Dupixent was found to be more effective in achieving an Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) and a reduction of ≥ 2 points from baseline to Week 16 compared with placebo. Additional studies established the efficacy of Dupixent in patients 6 to 17 years of age.[1,7,26]

Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP)

Two randomized, double-blind, multicenter, placebo-controlled studies evaluated the efficacy of Dupixent in adult patients with CRSwNP.[1,8-10] Patients enrolled in these studies were also treated with intranasal corticosteroids and had failed treatment with sino-nasal surgery or systemic corticosteroids (or were ineligible or intolerant to). Dupixent was found to significantly improve both the change from baseline to Week 24 in bilateral endoscopic nasal polyp score (NPS) and the change from baseline in the nasal congestion/obstruction score (averaged over 28 days) compared with placebo.

Guidelines

Asthma Guidelines

The Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention (2020) proposes a step-wise approach to asthma treatment.[11] The majority of patients can be managed with an ICS with or without a long-acting beta$_2$-agonist (LABA) and/or an additional controller. Dupixent is listed as an option for add-on therapy in patients ≥ 12 years of age with severe Type 2 asthma or asthma that requires treatment with an oral corticosteroid. Higher blood eosinophil levels and higher fractional concentration of exhaled nitric oxide (FeNO) may predict a good asthma response to Dupixent.

According to the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (2014; updated in 2020), severe asthma is defined as asthma which requires treatment with a high-dose ICS in addition to a second controller medication (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or asthma which remains uncontrolled despite this therapy.[12,23] Uncontrolled asthma is defined as asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids or asthma that meets one of the following four criteria:

5) Poor symptom control: Asthma Control Questionnaire consistently ≥ 1.5 or Asthma Control Test < 20;
6) Frequent severe exacerbations: two or more bursts of systemic corticosteroids in the previous year;
7) Serious exacerbations: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year;
8) Airflow limitation: FEV_1 80% predicted after appropriate bronchodilator witholding.

Atopic Dermatitis Guidelines

European consensus guidelines for the treatment of atopic dermatitis (2018) from multiple European dermatology associations, including the European Dermatology Forum (EDF), the European Academy of Dermatology and Venereology (EADV), and the European Academy of Allergy and Clinical Immunology (EAACI), recommend Dupixent as a disease-modifying drug for patients with moderate to severe atopic dermatitis, in whom topical treatment does not produce a sufficient response and other systemic treatment is not advisable.[13] These guidelines note that daily emollients should be used with Dupixent and it may be combined with other topical anti-inflammatory medications as needed. US guidelines do not address Dupixent.[14-16] However, they reinforce that most patients with atopic dermatitis can achieve disease control with non-pharmacologic interventions (e.g., emollients), standard topical anti-inflammatory therapies (e.g., topical corticosteroids, topical calcineurin inhibitors), and elimination of exacerbating factors.

Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP) Guidelines

A 2014 Practice Parameter on the Diagnosis and Management of Rhinosinusitis and a 2020 Practice Parameter for the Management of Rhinitis from the JTFPP recommend nasal corticosteroids be used in patients with chronic rhinosinusitis with nasal polyps, as they decrease nasal polyp size, prevent regrowth of nasal polyps following surgical removal, and improve nasal symptoms.[17-19,24] Short courses of oral corticosteroids are also recommended. Endoscopic surgical intervention may be considered as an adjunct to medical therapy in patients with chronic rhinosinusitis that is not responsive or is poorly responsive to medical therapy. Dupilumab is listed as a treatment option, but specific recommendations were not made. A 2015 Clinical Practice Guideline update on Adult Sinusitis from the American Academy of Otolaryngology makes similar recommendations, stating that clinicians should recommend saline nasal irrigation, topical intranasal corticosteroids, or both for symptom relief in patients with CRS (with or without nasal polyps).[20] Dupixent is not addressed.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Dupixent. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Dupixent as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Dupixent to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Dupixent is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Asthma.** Approve Dupixent for the duration noted if the patient meets one of the following conditions (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv and v):
     - **i.** Patient is ≥ 12 years of age; AND
     - **ii.** Patient meets ONE of the following criteria (a or b):
       - **a)** Patient has a blood eosinophil level ≥ 150 cells per microliter within the previous 6 weeks or within 6 weeks prior to treatment with any anti-interleukin therapy or Xolair; OR
         Note: Examples of anti-interleukin therapies include Dupixent, Nucala® (mepolizumab injection for subcutaneous use), Cinqair® (reslizumab injection for intravenous use), and Fasenra® (benralizumab injection for subcutaneous use).
       - **b)** Patient has oral (systemic) corticosteroid-dependent asthma according to the prescriber (e.g., the patient has received ≥ 5 mg oral prednisone or equivalent per day for ≥ 6 months); AND
     - **iii.** Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a and b):
       - **a)** An inhaled corticosteroid; AND
       - **b)** At least one additional asthma controller or asthma maintenance medication; AND

       Note: Examples of additional asthma controller or asthma maintenance medications are inhaled long-acting $beta_2$-agonists, inhaled long-acting muscarinic antagonists, leukotriene receptor antagonists, anti-interleukin-5 therapies (e.g., Cinqair, Fasenra, Nucala), and theophylline. Use of a combination inhaler containing both an inhaled corticosteroid and a long-acting $beta_2$-agonist would fulfil the requirement for both criteria a and b.
     - **iv.** Patient has asthma that is uncontrolled or was uncontrolled at baseline as defined by ONE of the following (a, b, c, d or e):
       - **a)** Patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR
       - **b)** Patient experienced one or more asthma exacerbation(s) requiring hospitalization or an Emergency Department visit in the previous year; OR
       - **c)** Patient has a forced expiratory volume in 1 second (FEV_1) < 80% predicted; OR
       - **d)** Patient has an FEV_1/forced vital capacity (FVC) < 0.80; OR
       - **e)** Patient has asthma that worsens upon tapering of oral corticosteroid therapy; AND

       Note: "Baseline" is defined as prior to receiving any Nucala or other anti-interleukin- 5 therapies (i.e., Fasenra or Nucala).
     - **v.** The medication is prescribed by or in consultation with an allergist, immunologist, or pulmonologist.

B) Patient is Currently Receiving Dupixent. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):

i. Patient has already received at least 6 months of therapy with Dupixent; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with Dupixent should be considered under criterion 1A (Asthma, Initial Therapy).

ii. Patient continues to receive therapy with one inhaled corticosteroid or one inhaled corticosteroid-containing combination inhaler; AND

iii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Dupixent therapy are decreased asthma exacerbations; decreased asthma symptoms; decreased hospitalizations or emergency department visits due to asthma; decreased requirement for oral corticosteroid therapy.

2. Atopic Dermatitis. Approve Dupixent for the duration noted if the patient meets one of the following conditions (A or B):

71. Initial Therapy. Approve for 4 months if the patient meets the following criteria (i, ii, and iii):

i. Patient is ≥ 6 years of age; AND

ii. Patient meets ONE of the following (a or b):

a) Patient has atopic dermatitis involvement estimated to be ≥ 10% of the body surface area (BSA) according to the prescriber and meets ALL of the following criteria ([1], [2], and [3]):

(1) Patient has tried at least one medium-, medium-high, high-, and/or super-high-potency prescription topical corticosteroid; AND

(2) This topical corticosteroid was applied daily for at least 28 consecutive days; AND

(3) Inadequate efficacy was demonstrated with this topical corticosteroid therapy, according to the prescriber; OR

b) Patient has atopic dermatitis involvement estimated to be < 10% of the body surface area (BSA) according to the prescriber and meets ALL of the following criteria ([1], [2], [3], and [4]):

(1) Patient has atopic dermatitis affecting ONLY the following areas: face, eyes/eyelids, skin folds, and/or genitalia; AND

(2) Patient has tried tacrolimus ointment (Protopic®, generics); AND

(3) Tacrolimus ointment (Protopic, generics) was applied daily for at least 28 consecutive days; AND

(4) Inadequate efficacy was demonstrated with tacrolimus ointment (Protopic, generics), according to the prescriber; AND

iii. The medication is prescribed by or in consultation with an allergist, immunologist, or dermatologist.

72. Patient is Currently Receiving Dupixent. Approve for 1 year if the patient meets the following criteria (i and ii):

i. Patient has already received at least 4 months of therapy with Dupixent; AND
Note: A patient who has received < 4 months of therapy or who is restarting therapy with Dupixent should be considered under criterion 2A (Atopic Dermatitis, Initial Therapy).

ii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Dupixent therapy are marked improvements in erythema, induration/papulation/edema, excoriations, and lichenification; reduced pruritus; decreased requirement for other topical or systemic therapies; reduced body surface area (BSA) affected with atopic dermatitis; or other responses observed.

3. Chronic Rhinosinusitis with Nasal Polyposis. Approve Dupixent for the duration noted if the patient meets one of the following conditions (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv and v):

i. Patient is ≥ 18 years of age; AND

ii. Patient is currently receiving therapy with an intranasal corticosteroid; AND

iii. Patient is experiencing significant rhinosinusitis symptoms such as nasal obstruction, rhinorrhea, or reduction/loss of smell according to the prescriber; AND

iv. Patient meets ONE of the following (a or b):

a) Patient has received treatment with a systemic corticosteroid within the previous 2 years or has a contraindication to systemic corticosteroid therapy; OR

b) Patient has had prior surgery for nasal polyps; AND

v. Dupixent is prescribed by or in consultation with an allergist, immunologist, or an otolaryngologist (ear, nose and throat [ENT] physician specialist).

B) Patient is Currently Receiving Dupixent. Approve for 1 year if the patient meets the following criteria (i, ii and iii):

i. Patient has already received at least 6 months of therapy with Dupixent; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with Dupixent should be considered under criterion 3A [Chronic Rhinosinusitis with Nasal Polyposis, Initial Therapy]).

ii. Patient continues to receive therapy with an intranasal corticosteroid; AND

iii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Dupixent therapy are reduced nasal polyp size, improved nasal congestion, reduced sinus opacification, decreased sino-nasal symptoms, improved sense of smell.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Dupixent is not recommended in the following situations:

50. Concurrent use of Dupixent with another Anti-Interleukin Monoclonal Antibody. The efficacy and safety of Dupixent in combination with other anti-interleukin monoclonal antibodies (e.g., Cinqair, Nucala, Fasenra) have not been established.

51. Concurrent use of Dupixent with Xolair® (omalizumab injection for subcutaneous use). Xolair is a recombinant humanized immunoglobulin G (IgG)1κ monoclonal antibody indicated for use in patients ≥ 6 years of age with moderate to severe persistent asthma and who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.[21] Xolair is also indicated for chronic idiopathic urticaria in adults and adolescents 12 years of age and older who remain symptomatic despite H_1 antihistamine treatment and for nasal polyps, as add-on maintenance treatment in patients ≥ 18 years of age with an inadequate response to nasal corticosteroids. The efficacy and safety of Dupixent used in combination with Xolair have not been established.

52. Eosinophilic Esophagitis. One small, phase II study (n = 45) evaluated the efficacy of Dupixent in patients with active eosinophilic esophagitis.[27] Compared with placebo, Dupixent was found to reduce dysphagia, histologic features of disease, and abnormal endoscopic features. There areongoing Phase III studies that are evaluating the use of Dupixent in pediatric and adult patients with eosinoiphilic esophagitis. Results are anticipated in 2022.[22] Guidelines for the management of eosinophilic esophagitis from the American Gastroenterological Association (AGA) and the Joint Task Force on Allergy-Immunology Practice Parameters (2020) only recommend using anti-interleukin-5 therapies in the context of a clinical trial.[25]

53. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	• Updated initial therapy criteria for "Asthma in Patients with Moderate to Severe Disease" to state that the blood eosinophil level requirement of ≥ 150 cells per microliter should be from a level prior to treatment with Xolair, as well as prior to treatment with any anti-interleukin (IL) agent. Previously criteria only noted the level should be prior to any anti-IL therapy. • Updated initial therapy criteria for "Asthma in Patients with Moderate to Severe Disease" to more concisely state the previous therapies required. Added the following note: An exception to the requirement for a trial of one additional asthma controller/maintenance medication (criterion b) can be made if the patient has already received anti-IL-5 therapy (e.g., Cinqair, Fasenra, Nucala) or Xolair used concomitantly with an ICS for at least 3 consecutive months. • Updated initial therapy criteria for "Asthma in Patients with Moderate to Severe Disease" to state that the patient's asthma is uncontrolled or was uncontrolled prior to starting any anti-IL therapy (e.g., Cinqair, Fasenra, Nucala, Dupixent) or Xolair. Previously criteria only stated it should be uncontrolled prior to anti-IL therapy.	01/23/2019
Selected Revision	Changed the age requirement for "Atopic Dermatitis, Moderate to Severe" from ≥ 18 years of age to ≥ 12 years of age.	03/12/2019
Selected Revision	• Asthma: Approval indication was changed from "Asthma in Patients with Moderate to Severe Disease" to "Asthma". Wording in reference to "according to the prescribing physician" was changed to "according to the prescriber". • Atopic Dermatitis: Approval indication was changed from "Atopic Dermatitis, Moderate to Severe" to "Atopic Dermatitis". Duration of initial approval was clarified to 4 months (previously 16 weeks). Wording in reference to "according to the prescribing physician" was changed to "according to the prescriber". • Chronic Rhinosinusitis with Nasal Polyposis: Added new approval criteria for this indication which include an age requirement, involvement of a specialist, current intranasal corticosteroid therapy, the presence of significant rhinosinusitis symptoms, and previous systemic therapy (or contraindication) or surgery for nasal polyps. • Conditions Not Recommended for Approval: Removed "Nasal Polyps".	07/10/2019
Annual Revision	• Asthma: Removed lists of examples of inhaled asthma controller/maintenance medications.	02/12/2020
Selected Revision	• Added the following to the Policy Statement: All reviews will be forwarded to a Pharmacist.	03/25/2020
Selected Revision	• Atopic Dermatitis: Age requirement changed from ≥ 12 years of age to ≥ 6 years of age.	06/03/2020
Selected Revision	• Updated the Policy Statement to: All reviews will be forwarded to a Pharmacist or Medical Director.	6/10/2020
Update	Date: 06/16/2020 • Asthma: No criteria changes. Removed "urgent care and medical visits" from the examples of a response to Dupixent therapy in the criteria for Patients Continuing Dupixent Therapy.	NA
Selected Revision	• Updated the Policy Statement to remove: All reviews will be forwarded to a Pharmacist or Medical Director.	07/29/2020
Annual Revision	No criteria changes.	02/17/2021

PRIOR AUTHORIZATION POLICY

POLICY: Immunologicals – Fasenra Prior Authorization Policy

- Fasenra® (benralizumab injection for subcutaneous use – AstraZeneca)

REVIEW DATE: 02/17/2021

OVERVIEW

Fasenra, an interleukin-5 receptor alpha (IL-5Rα)-directed cytolytic monoclonal antibody, is indicated for **severe asthma** as add-on maintenance treatment of patients ≥ 12 years of age who have an eosinophilic phenotype.[1] Limitations of Use: Fasenra is not indicated for the treatment of other eosinophilic conditions or for the relief of acute bronchospasm/status asthmaticus.

Clinical Efficacy

Two of the Fasenra pivotal trials included patients 12 to 75 years of age with severe asthma not controlled with inhaled corticosteroid (ICS)/long-acting beta$_2$-agonist (LABA) therapy.[2-4] The addition of Fasenra to existing therapy significantly reduced annualized asthma exacerbation rates in patients with baseline blood eosinophil levels ≥ 300 cells/microliter. The magnitude of the improvements observed with Fasenra in this patient population were larger than those observed in patients with lower baseline eosinophil levels (e.g., < 150 cells/microliter). Another pivotal study involved adults with severe asthma receiving high-dose ICS/LABA and chronic oral corticosteroid (OCS) therapy who had a baseline blood eosinophil level ≥ 150 cells/microliter.[4] At Week 28, significantly more patients receiving Fasenra were able to reduce their OCS dose compared with placebo.

Guidelines

The Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention (2020) proposes a step-wise approach to asthma treatment.[5] Fasenra is listed as an option for add-on therapy in patients ≥ 12 years of age with difficult-to-treat, severe eosinophilic asthma (i.e., asthma that cannot be managed by therapy with an ICS/LABA combination with or without an additional controller). Higher blood eosinophil levels, more exacerbations in the previous year, adult-onset asthma, nasal polyposis, and maintenance oral corticosteroids at baseline may predict a good asthma response to Fasenra.

According to the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (2014; updated in 2020), severe asthma is defined as asthma which requires treatment with a high-dose ICS in addition to a second controller medication (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or asthma which remains uncontrolled despite this therapy.[6,7] Uncontrolled asthma is defined as asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids or asthma that meets one of the following four criteria:

9) Poor symptom control: Asthma Control Questionnaire consistently ≥ 1.5 or Asthma Control Test < 20;
10) Frequent severe exacerbations: two or more bursts of systemic corticosteroids in the previous year;
11) Serious exacerbations: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year;
12) Airflow limitation: FEV_1 < 80% predicted after appropriate bronchodilator withholding.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Fasenra. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Fasenra as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Fasenra to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Fasenra is recommended in those who meet the following criteria:

FDA-Approved Indications

11. Asthma. Approve Fasenra for the duration noted if the patient meets one of the following conditions (A or B):

73. Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv, and v):

- **i.** Patient is ≥ 12 years of age; AND
- **ii.** Patient has a blood eosinophil count ≥ 150 cells per microliter within the previous 6 weeks or within 6 weeks prior to treatment with any anti-interleukin-5 therapy; AND
  Note: Examples of anti-interleukin-5 therapies include Fasenra, Cinqair® (reslizumab injection for intravenous use), and Nucala® (mepolizumab injection for subcutaneous use).
- **iii.** Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a and b):
  - **a)** An inhaled corticosteroid; AND
  - **b)** At least one additional asthma controller or asthma maintenance medication; AND

  Note: Examples of additional asthma controller or asthma maintenance medications are inhaled long-acting beta$_2$-agonists, inhaled long-acting muscarinic antagonists, leukotriene receptor antagonists, anti-interleukin-5 therapies (e.g., Cinqair, Fasenra, Nucala), and theophylline. Use of a combination inhaler containing both an inhaled corticosteroid and a long-acting beta$_2$-agonist would fulfil the requirement for both criteria a and b.
- **iv.** Patient has asthma that is uncontrolled or was uncontrolled at baseline as defined by ONE of the following (a, b, c, d, or e):
  - **a)** Patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR
  - **b)** Patient experienced one or more asthma exacerbation(s) requiring hospitalization or an Emergency Department visit in the previous year; OR
  - **c)** Patient has a forced expiratory volume in 1 second (FEV_1) < 80% predicted; OR
  - **d)** Patient has an FEV_1/forced vital capacity (FVC) < 0.80; OR
  - **e)** The patient has asthma that worsens upon tapering of oral corticosteroid therapy; AND

  Note: "Baseline" is defined as prior to receiving any Fasenra or other anti-interleukin- 5 therapies (i.e., Cinqair or Nucala).
- **v.** The medication is prescribed by or in consultation with an allergist, immunologist, or pulmonologist.

74. Patient is Currently Receiving Fasenra. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):

- **i.** Patient has already received at least 6 months of therapy with Fasenra; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with Fasenra should be considered under criterion 1A (Asthma, Initial Therapy).

ii. Patient continues to receive therapy with one inhaled corticosteroid or one inhaled corticosteroid-containing combination inhaler; AND

iii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Fasenra therapy are decreased asthma exacerbations; decreased asthma symptoms; decreased hospitalizations, emergency department/urgent care, or medical clinic visits due to asthma; and decreased requirement for oral corticosteroid therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Fasenra is not recommended in the following situations:

54. Chronic Obstructive Pulmonary Disease (COPD). Fasenra is not indicated for the treatment of COPD.[1] One double-blind, placebo-controlled, Phase IIa study (n = 101) evaluated the efficacy and safety of Fasenra in patients 40 to 80 years of age with eosinophilia and moderate to severe COPD.[8] The annualized rate of acute COPD exacerbations was not reduced with Fasenra compared with placebo. Lung function was also not significantly improved with Fasenra vs. placebo. Numerically greater (although non-significant) improvements in exacerbations and lung function were observed with Fasenra vs. placebo in patients with baseline blood eosinophil levels of 200 cells/microliter or more. Two double-blind, placebo-controlled, Phase III studies (GALATHEA and TERRANOVA) also evaluated Fasenra in patients with moderate to very severe COPD (n = 1,120 and n = 1,545 patients, respectively, with eosinophils ≥ 220 cells/mm^3).[9] Following, 56 weeks of therapy, the annualized COPD exacerbation rates were not statistically significantly reduced with Fasenra vs. placebo in either study. Current COPD guidelines from the Global Initiative for Chronic Lung Disease (GOLD) [2021] note the negative data with Fasenra and state that further studies are needed.[10]

55. Concurrent use of Fasenra with Another Anti-Interleukin Monoclonal Antibody. The efficacy and safety of Fasenra used in combination with other anti-interleukin monoclonal antibodies (e.g., Nucala® [mepolizumab injection for subcutaneous use], Cinqair® [reslizumab injection for intravenous use], Dupixent® [dupilumab subcutaneous injection]) have not been established.

56. Concurrent use of Fasenra with Xolair® (omalizumab injection for subcutaneous use). Xolair is a recombinant humanized immunoglobulin G (IgG)1κ monoclonal antibody indicated for use in adults and adolescents (aged ≥ 6 years) with moderate to severe persistent asthma and who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICSs.[11] Xolair is also indicated for chronic idiopathic urticaria in adults and adolescents 12 years of age and older who remain symptomatic despite H_1 antihistamine treatment and for nasal polyps, as add-on maintenance treatment in patients ≥ 18 years of age with an inadequate response to nasal corticosteroids. The efficacy and safety of Fasenra used in combination with Xolair have not been established.

57. Hypereosinophilic Syndrome. Fasenra is not indicated for the treatment of eosinophilic conditions other than asthma.[1] A small, randomized, double-blind, placebo-controlled, Phase II trial (n = 20) evaluated the efficacy of Fasenra in patients who had platelet-derived growth factor receptor alpha (PDGFRA)-negative hypereosinophilic syndrome with an absolute eosinophil count of 1,000 cells/mm^3.[12] At Week 12, 90% of patients receiving Fasenra (n = 9/10) vs. 30% of patients receiving placebo (n = 3/10) achieved a 50% or greater reduction in the absolute eosinophil count (P = 0.02). Following the randomized phase, all patients received open-label Fasenra 30 mg every 4 weeks. During this time, 74% of patients (n = 14/19) had sustained clinical and hematologic responses for 48 weeks.

The 2019 World Health Organization (WHO)-defined eosinophilic disorders update on diagnosis, risk stratification, and management notes that corticosteroids remain the cornerstone of therapy for several forms of hypereosinophilic syndrome.[13] Use of anti-interleukin (IL)-5 approaches for the treatment of hypereosinophilic syndrome remains investigational. In patients who have idiopathic hypereosinophilic syndrome and end organ damage, enrollment into an anti-IL-5/anti-IL-5 receptor antibody clinical trial is recommended as second-line therapy. Similarly, in patients with lymphocyte-variant hypereosinophilic syndrome, enrollment into an anti-IL-5/anti-IL-5 receptor antibody clinical trial is also recommended as second-line therapy. Further investigation is warranted.

58. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	Updated initial therapy criteria for "Asthma in Patients with Severe Disease and an Eosinophilic Phenotype" to more concisely state the previous therapies required. Added the following note: An exception to the requirement for a trial of one additional asthma controller/maintenance medication (criterion b) can be made if the patient has already received anti-IL-5 therapy (e.g., Cinqair, Fasenra, Nucala) used concomitantly with an ICS for at least 3 consecutive months.	01/23/2019
Update	Added data regarding Fasenra for the treatment of COPD and hypereosinophilic syndrome. Date: 06/24/2019.	--
Annual Revision	• **Asthma**: Approval indication was changed from "Asthma in Patients with Severe Disease and an Eosinophilic Phenotype" to "Asthma". Wording in reference to "according to the prescribing physician" was changed to "according to the prescriber". Removed lists of examples of inhaled asthma controller/maintenance medications. • **Hypereosinophilic Syndrome**: Condition not recommended for approval was changed from "Hypereosinophilic Syndrome, Idiopathic" to "Hypereosinophilic Syndrome".	02/12/2020
Annual Revision	No criteria changes.	02/17/2021

IL – Interleukin; ICS – Inhaled corticosteroid; COPD – Chronic obstructive pulmonary disease.

PRIOR AUTHORIZATION POLICY

POLICY: Immunologicals – Nucala Prior Authorization Policy

- Nucala® (mepolizumab injection for subcutaneous use – GlaxoSmithKline)

REVIEW DATE: 02/17/2021

OVERVIEW

Nucala, an interleukin-5 antagonist monoclonal antibody, is indicated for the following uses:[1]

- **Asthma**, as add-on maintenance treatment of patients ≥ 6 years of age with severe disease and an eosinophilic phenotype. Limitations of Use: Nucala is not indicated for the relief of acute bronchospasm or status asthmaticus.
- **Eosinophilic granulomatosis with polyangiitis** (EGPA) [formerly known as Churg-Strauss Syndrome] in adult patients.
- **Hypereosinophilic syndrome** (HES) in patients ≥ 12 years of age who have had HES for ≥ 6 months without an identifiable non-hematologic secondary cause.

Clinical Efficacy

Asthma

The efficacy of Nucala was established in three studies in patients ≥ 12 years of age with severe asthma and eosinophilic inflammation despite therapy with an inhaled corticosteroid and another maintenance medication.[1-4] In general, patients were required to have elevated eosinophils at baseline (e.g., peripheral blood eosinophil count ≥ 150 cells/microliter at screening or ≥ 300 cells/microliter at some time during the previous year). In patients with a history of frequent exacerbations (i.e., two or more asthma exacerbations requiring systemic corticosteroid therapy within the previous year), Nucala significantly reduced the rate of clinically significant asthma exacerbations per patient per year compared with placebo. Additionally, in a study of patients with asthma requiring maintenance treatment with oral corticosteroids, significantly more patients who received 24 weeks of Nucala therapy were able to reduce their oral corticosteroid dose compared with placebo. Use of Nucala in patients 6 to 11 years of age with severe eosinophilic asthma is supported by the clinical trials in adults and adolescents along with additional pharmacokinetic, pharmacodynamic, and safety studies conducted specifically in patients 6 to 11 years of age.

Eosinophilic Granulomatosis with Polyangiitis (EGPA)
One study evaluated the efficacy of Nucala in patients ≥ 18 years of age with relapsing or refractory EGPA who had received ≥ 4 weeks of a stable oral corticosteroid dose (i.e., prednisolone, prednisone).[5] Patients were also required to have a baseline relative eosinophil level of 10% or an absolute eosinophil level > 1,000 cells per microliter; however, the baseline mean absolute eosinophil level was approximately 175 cells per microliter across both treatment groups. While remission benefit of Nucala was demonstrated in the overall patient population, the magnitude of improvements observed with Nucala were larger in patients with baseline eosinophil levels ≥ 150 cells per microliter than in patients with lower baseline levels.

Hypereosinophilic Syndrome
One study evaluated the efficacy of Nucala in patients ≥ 12 years of age with hypereosinophilic syndrome for ≥ 6 months.[6] Patients with non-hematologic secondary hypereosinophilic syndrome and those with FIP1L1-PDGFRα kinase-positive hypereosinophilic syndrome were excluded. All patients had a baseline blood eosinophil count ≥ 1,000 cells per microliter and had experienced two or more hypereosinophilic flares within the previous 12 months. Additionally, all patients had been on stable therapy for their hypereosinophilic syndrome (e.g., oral corticosteroids, immunosuppressive agents, or cytotoxic therapy) for 4 weeks or more prior to randomization. Over the 32-week treatment period, significantly fewer patients experienced one or more hypereosinophilic syndrome flares with Nucala compared with placebo.

Guidelines
Asthma Guidelines
The Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention (2020) proposes a step-wise approach to asthma treatment.[7] Nucala is listed as an option for add-on therapy in patients ≥ 6 years of age with difficult-to-treat, severe eosinophilic asthma (i.e., asthma that cannot be managed by therapy with an ICS/long-acting beta$_2$-agonist [LABA] combination with or without an additional controller). Higher blood eosinophil levels, more exacerbations in the previous year, adult-onset asthma, nasal polyposis, and maintenance corticosteroids at baseline may predict a good asthma response to Nucala.

According to the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (2014; updated in 2020), severe asthma is defined as asthma which requires treatment with a high-dose ICS in addition to a second controller medication (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or asthma which remains uncontrolled despite this therapy.[8,9] Uncontrolled asthma is defined as asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids or asthma that meets one of the following four criteria:

13) Poor symptom control: Asthma Control Questionnaire consistently ≥ 1.5 or Asthma Control Test < 20;
14) Frequent severe exacerbations: two or more bursts of systemic corticosteroids in the previous year;
15) Serious exacerbations: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year;
16) Airflow limitation: FEV_1 < 80% predicted after appropriate bronchodilator withholding.

EGPA Guidelines
Current EGPA guidelines do not address Nucala or the other anti-interleukin (IL)-5 therapies. The 2016 European League Against Rheumatism (EULAR) recommendations for the management of anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis address EGPA.[10] All patients should be managed in close collaboration with or at centers of expertise where specialists can provide appropriate interventions and monitoring. For remission-induction in patients with new onset organ- or life-threatening ANCA-associated vasculitis, a combination of corticosteroids and either cyclophosphamide or rituximab is recommended (Level 3 evidence, Grade C recommendation for EGPA specifically). For maintenance of

remission of EGPA, a combination of low-dose corticosteroids and azathioprine should be used (Level 3 evidence, Grade C recommendation); maintenance therapy should be considered for 24 months at a minimum.

In 2015, a Consensus Task Force comprised of experts from Europe and the United States published recommendations for the evaluation and management of EGPA.[11] These recommendations are similar to the EULAR guidance and also conclude that EGPA should be managed in collaboration with, or in, centers specializing in the management of small- and medium-sized-vessel vasculitides. In general, it is appropriate to use corticosteroids to induce EGPA remission; these medications are the cornerstone of therapy for EGPA.

Hypereosinophilia Guidelines

The 2019 World Health Organization (WHO)-defined eosinophilic disorders update on diagnosis, risk stratification, and management notes that corticosteroids remain the cornerstone of therapy for several forms of HES.[12] Use of anti-IL-5 approaches for the treatment of HES remains investigational. This document was published prior to the approval of Nucala for HES. However, it is recommended that patients with idiopathic HES and end organ damage as well as those with lymphocyte-variant HES should consider enrollment into an anti-IL-5/anti-IL-5 receptor antibody clinical trial (as second-line therapy).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Nucala. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Nucala as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Nucala to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nucala is recommended in those who meet the following criteria:

FDA-Approved Indications

12. Asthma. Approve Nucala for the duration noted if the patient meets one of the following conditions (A or B):

75. Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv, and v):

- **i.** Patient is ≥ 6 years of age; AND
- **ii.** Patient has a blood eosinophil level ≥ 150 cells per microliter within the previous 6 weeks or within 6 weeks prior to treatment with any anti-interleukin-5 therapy; AND
  Note: Examples of anti-interleukin-5 therapies include Nucala, Cinqair® (reslizumab injection for intravenous use), and Fasenra® (benralizumab injection for subcutaneous use).
- **iii.** Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a and b):
  - **a)** An inhaled corticosteroid; AND
  - **b)** At least one additional asthma controller or asthma maintenance medication; AND

  Note: Examples of additional asthma controller or asthma maintenance medications are inhaled long-acting beta$_2$-agonists, inhaled long-acting muscarinic antagonists, leukotriene receptor antagonists, anti-interleukin-5 therapies (e.g., Cinqair, Fasenra, Nucala), and

theophylline. Use of a combination inhaler containing both an inhaled corticosteroid and a long-acting beta$_2$-agonist would fulfil the requirement for both criteria a and b.

iv. Patient has asthma that is uncontrolled or was uncontrolled at baseline as defined by ONE of the following (a, b, c, d, or e):

a) Patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR

b) Patient experienced one or more asthma exacerbation(s) requiring hospitalization or an Emergency Department visit in the previous year; OR

c) Patient has a forced expiratory volume in 1 second (FEV_1) < 80% predicted; OR

d) Patient has an FEV_1/forced vital capacity (FVC) < 0.80; OR

e) The patient has asthma that worsens upon tapering of oral corticosteroid therapy; AND

Note: "Baseline" is defined as prior to receiving any Nucala or other anti-interleukin-5 therapies (i.e., Fasenra or Nucala).

v. The medication is prescribed by or in consultation with an allergist, immunologist, or pulmonologist.

76. Patient is Currently Receiving Nucala. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):

i. Patient has already received at least 6 months of therapy with Nucala; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with Nucala should be considered under criterion 1A (Asthma, Initial Therapy).

ii. Patient continues to receive therapy with one inhaled corticosteroid or one inhaled corticosteroid-containing combination inhaler; AND

iii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Nucala therapy are decreased asthma exacerbations; decreased asthma symptoms; decreased hospitalizations, emergency department/urgent care, or medical clinic visits due to asthma; and decreased requirement for oral corticosteroid therapy.

13. Eosinophilic Granulomatosis with Polyangiitis (EGPA) [formerly known as Churg-Strauss Syndrome]. Approve Nucala for the duration noted if the patient meets one of the following conditions (A or B):

14. Initial Therapy. Approve for 6 months if the patient meets the following conditions (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Patient has/had a blood eosinophil level ≥ 150 cells per microliter within the previous 6 weeks or within 6 weeks prior to treatment with any anti-interleukin-5 therapy; AND
Note: Examples of anti-interleukin-5 therapies include Nucala, Cinqair, and Fasenra.

iii. Patient has tried therapy with a corticosteroid (e.g., prednisone) for a minimum of 4 weeks; AND

iv. The medication is prescribed by or in consultation with an allergist, immunologist, pulmonologist, or rheumatologist.

15. Patient is Currently Receiving Nucala. Approve for 1 year if the patient meets the following criteria (i and ii):

i. Patient has already received at least 6 months of therapy with Nucala; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with Nucala should be considered under criterion 2A (Eosinophilic Granulomatosis with Polyangiitis, Initial Therapy).

ii. Patient has responded to therapy as determined by the prescriber.
Note: Examples of a response to Nucala therapy are reduced rate of relapse, corticosteroid dose reduction, and reduced eosinophil levels.

16. **Hypereosinophilic Syndrome.** Approve Nucala for the duration noted if the patient meets one of the following conditions (A or B):
    17. Initial Therapy. Approve for 8 months if the patient meets the following conditions (i, ii, iii, iv, v, vi, and vii):
        - **i.** Patient is ≥ 12 years of age; AND;
        - **ii.** Patient has had hypereosinophilic syndrome for ≥ 6 months; AND
        - **iii.** Patient has FIP1L1-PDGFRα-negative disease; AND
        - **iv.** Patient does NOT have an identifiable non-hematologic secondary cause of hypereosinophilic syndrome according to the prescriber; AND
          Note: Examples of secondary causes of hypereosinophilic syndrome include drug hypersensitivity, parasitic helminth infection, human immunodeficiency virus infection, non-hematologic malignancy.
        - **v.** Patient has/had a blood eosinophil level ≥ 1,000 cells per microliter prior to treatment with any anti-interleukin-5 therapy; AND
          Note: Examples of anti-interleukin-5 therapies include Nucala, Cinqair, and Fasenra.
        - **vi.** Patient has tried at least one other treatment for hypereosinophilic syndrome for a minimum of 4 weeks; AND
          Note: Treatments for hypereosinophilic syndrome include systemic corticosteroids, hydroxyurea, cyclosporine, imatinib, methotrexate, tacrolimus, and azathioprine.
        - **vii.** Nucala is prescribed by or in consultation with an allergist, immunologist, pulmonologist, or rheumatologist.
    18. Patient is Currently Receiving Nucala. Approve for 1 year if the patient meets the following criteria (i and ii):
        - **i.** Patient has already received at least 8 months of therapy with Nucala; AND
          Note: A patient who has received < 8 months of therapy or who is restarting therapy with Nucala should be considered under criterion 3A (Hypereosinophilic Syndrome, Initial Therapy).
        - **ii.** Patient has responded to therapy as determined by the prescriber.
          Note: Examples of a response to Nucala therapy are decreased number of flares, improved fatigue, reduced corticosteroid requirements, and decreased eosinophil levels.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nucala is not recommended in the following situations:

59. **Atopic Dermatitis.** Nucala is not indicated for the treatment of atopic dermatitis.[1] In one small study, intravenous (IV) mepolizumab significantly reduced peripheral blood eosinophil counts in patients with moderate to severe atopic dermatitis.[13,14] However, mepolizumab IV therapy did not result in clinical success as assessed by Physician's Global Assessment of Improvement scores compared with placebo. Other clinical outcomes were also not significantly improved with mepolizumab IV. Another small study evaluated subcutaneous Nucala in patients with moderate to severe atopic dermatitis.[15] Following 16 weeks of therapy, Nucala did not demonstrate efficacy, with 11% (n = 2/11) of patients meeting the primary endpoint of treatment success with Nucala vs. 0 with placebo.

60. **Chronic Obstructive Pulmonary Disease (COPD).** Nucala is not indicated for the treatment of COPD.[1] Two Phase III studies, METREX (n = 836) and METREO (n = 675) evaluated Nucala in patients with COPD who had a history of moderate or severe exacerbations despite treatment with inhaled triple therapy (inhaled corticosteroid/long-acting muscarinic antagonist/long-acting beta$_2$-agonist).[16] METREX included patients regardless of eosinophil counts, but did include a subgroup of patients who were considered to have an eosinophilic phenotype (eosinophil count ≥ 150 cells/microliter) [n = 462]. METREO only included patients with an eosinophilic phenotype (defined

as an eosinophil count ≥ 150 cells/microliter at screening or ≥ 300 cells/microliter within the previous year). Overall, lower COPD exacerbation rates were observed with Nucala vs. placebo; however, none of these reductions were statistically significant in either the METREX overall modified intent to treat (mITT) population or the METREO mITT population (which included all eosinophilic phenotype patients). In the subgroup of patients in the METREX study with an eosinophilic phenotype, the COPD exacerbation rates were statistically lower with Nucala vs. placebo, as was the difference in the time to first exacerbation. In July 2018, the FDA's Pulmonary Allergy Drugs Advisory Committee voted against approval of Nucala as an add-on treatment to inhaled corticosteroid-based maintenance treatments to reduce flare-ups in patients with COPD.[17] The Committee had concerns about the defining criteria for the eosinophilic phenotype of COPD as well as the lack of data on patient asthma history. Subsequently, in September 2018, the FDA rejected the approval of Nucala for COPD citing the need for additional clinical data. Current COPD guidelines from the Global Initiative for Chronic Lung Disease (GOLD) [2021] note the mixed data with Nucala.[18] The guidelines state that further studies are needed to determine if Nucala may have a role in a highly selected subgroup of patients with eosinophilic COPD.

61. Concurrent use of Nucala with another Anti-Interleukin Monoclonal Antibody. The efficacy and safety of Nucala used in combination with other anti-interleukin monoclonal antibodies (e.g., Cinqair, Fasenra, Dupixent® [dupilumab subcutaneous injection]) have not been established.

62. Concurrent use of Nucala with Xolair® (omalizumab injection for subcutaneous use). Xolair is a recombinant humanized immunoglobulin G (IgG)1κ monoclonal antibody indicated for use in patients ≥ 6 years of age with moderate to severe persistent asthma and who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICSs.[19] Xolair is also indicated for chronic idiopathic urticaria in adults and adolescents 12 years of age and older who remain symptomatic despite H_1 antihistamine treatment and for nasal polyps, as add-on maintenance treatment in patients ≥ 18 years of age with an inadequate response to nasal corticosteroids. The efficacy and safety of Nucala used in combination with Xolair have not been established. A small number of case reports detailing combination use of Nucala and Xolair are available for both FDA-approved and off-label uses.[20-22] Further investigation is warranted.

63. Eosinophilic Esophagitis, Eosinophilic Gastroenteritis, or Eosinophilic Colitis. Nucala is not indicated for the treatment of eosinophilic esophagitis, eosinophilic gastroenteritis or eosinophilic colitis.[1] A few small studies have reported IV mepolizumab to be efficacious in these conditions.[23-25] Of note, Nucala is not approved for IV administration.[1] Guidelines for the management of eosinophilic esophagitis from the American Gastroenterological Association (AGA) and the Joint Task Force on Allergy-Immunology Practice Parameters (2020) only recommend using anti-interleukin-5 therapies in the context of a clinical trial.[26] Further research is warranted to determine if Nucala has a place in therapy in the treatment of these conditions.

64. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Updated initial therapy criteria for "Asthma in Patients with Severe Disease and an Eosinophilic Phenotype" to more concisely state the previous therapies required. Added the following note: An exception to the requirement for a trial of one additional asthma controller/maintenance medication (criterion b) can be made if the patient has already received anti-IL-5 therapy (e.g., Cinqair, Fasenra, Nucala) used concomitantly with an ICS for at least 3 consecutive months.	01/23/2019
Selected Revision	• **Asthma**: Approval indication was changed from "Asthma in Patients with Severe Disease and an Eosinophilic Phenotype" to "Asthma". Age approval changed from ≥ 12 years of age to ≥ 6 years of age. Wording in reference to "according to the	09/25/2019

	prescribing physician" was changed to "according to the prescriber". Added Wixela Inhub, a generic to Advair Diskus, to list of examples of asthma controller/maintenance medications. • **EGPA**: Wording in reference to "according to the prescribing physician" was changed to "according to the prescriber".	
Annual Revision	• **Asthma**: Removed lists of examples of inhaled asthma controller/maintenance medications. • **Hypereosinophilic Syndrome**: Condition not recommended for approval was changed from "Hypereosinophilic Syndrome, Idiopathic" to "Hypereosinophilic Syndrome".	02/12/2020
Selected Revision	• Added "Hypereosinophilic Syndrome" to "FDA-Approved Indications". • Removed "Hypereosinophilic Syndrome" from "Conditions Not Recommended for Approval".	10/28/2020
Annual Revision	"Nasal Polyps" removed from "Conditions Not Recommended for Approval".	02/17/2021

IL – Interleukin; ICS – Inhaled corticosteroid; EGPA – Eosinophilic granulomatosis with polyangiitis.

PRIOR AUTHORIZATION POLICY

POLICY: Immunologicals – Xolair Prior Authorization Policy

- Xolair® (omalizumab injection for subcutaneous use – Genentech/Novartis)

REVIEW DATE: 02/17/2021

OVERVIEW

Xolair, an anti-immunoglobulin E (IgE) monoclonal antibody, is indicated in the following conditions:[1]

- **Asthma,** in patients ≥ 6 years of age with moderate to severe persistent disease who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids (ICSs). Xolair has been shown to decrease the incidence of asthma exacerbations in these patients. Limitations of Use: Xolair is not indicated for the relief of acute bronchospasm or status asthmaticus. It is also not indicated for the treatment of other allergic conditions.
- **Chronic idiopathic urticaria**, in patients ≥ 12 years of age who remain symptomatic despite H1 antihistamine treatment. Limitation of Use: Xolair is not indicated for the treatment of other forms of urticaria.
- **Nasal polyps**, as add-on maintenance treatment in patients ≥ 18 years of age with an inadequate response to nasal corticosteroids.

Dosing of Xolair for the treatment of asthma or nasal polyps is based on body weight and the serum total immunoglobulin E (IgE) level measured before the start of treatment.[1] Dosing for these indications is only provided for patients with a pretreatment serum IgE level ≥ 30 IU/mL. Dosing of Xolair in patients with chronic idiopathic urticaria is not dependent on serum IgE level or body weight.

Clinical Efficacy

Asthma Clinical Efficacy

In general, the pivotal studies in which Xolair demonstrated its efficacy for the treatment of asthma included patients with moderate to severe allergic asthma who had a positive skin test to perennial aeroallergens.[1-11] Patients also had a baseline IgE level between 30 and 700 IU/mL and were experiencing asthma symptoms despite ICS therapy (with or without a second controller such as an inhaled long-acting $beta_2$-agonist [LABA]). There are data to support the use of Xolair in patients ≥ 6 years of age. In the majority of the Xolair trials, efficacy was assessed as early as 16 weeks.

Chronic Idiopathic Urticaria Clinical Efficacy

Efficacy and safety of Xolair in the treatment of chronic idiopathic urticaria was established in two pivotal studies in patients 12 to 75 years of age who had symptomatic chronic idiopathic urticaria despite having used an H1-receptor antagonist for ≥ 2 weeks.[1,12,13] Chronic idiopathic urticaria was defined as a patient having hives, angioedema, or both that recur for > 6 weeks and have no apparent external trigger. One of the studies included a 12-week double-blind treatment period, while the other was longer with 24 weeks of double-blind treatment.

Nasal Polyps Clinical Efficacy

Two pivotal studies evaluated the efficacy of Xolair in patients ≥ 18 years of age with persistent bilateral nasal polyps, despite treatment with intranasal corticosteroids.[1,14] Patients were also required to have nasal congestion, impaired health-related quality of life, and a serum IgE level between 30 IU/mL and 1,500 IU/mL. There was no requirement for prior systemic corticosteroid treatment or prior surgery. However, 60% of patients had previously undergone nasal polyp surgery and 22% of patients reported use of a systemic corticosteroid in the previous year. Patients continued treatment with intranasal corticosteroids throughout the study. Across both studies, efficacy was evaluated at Week 24.

Guidelines

Asthma Guidelines

The Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention (2020) proposes a step-wise approach to asthma treatment.[15] Xolair is listed as an option for add-on therapy in patients ≥ 6 years of age with moderate or severe allergic asthma that is uncontrolled by medium- to high-dose ICS/LABA therapy.

According to the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (2014; updated in 2020), severe asthma is defined as asthma which requires treatment with a high-dose ICS in addition to a second controller medication (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or asthma which remains uncontrolled despite this therapy.[16,17] Uncontrolled asthma is defined as asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids or asthma that meets one of the following four criteria:

17) Poor symptom control: Asthma Control Questionnaire consistently ≥ 1.5 or Asthma Control Test < 20;
18) Frequent severe exacerbations: two or more bursts of systemic corticosteroids in the previous year;
19) Serious exacerbations: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year;
20) Airflow limitation: FEV_1 < 80% predicted after appropriate bronchodilator withholding.

Chronic Urticaria Guidelines

A Practice Parameter on the Diagnosis and Management of Acute and Chronic Urticaria from the Joint Task Force on Practice Parameters (JTFPP), representing the American Academy of Allergy, Asthma, & Immunology (AAAAI); the American College of Allergy, Asthma, & Immunology (ACAAI); and the Joint Council of Allergy, Asthma, & Immunology (JCAAI) [2014] and guideline from the European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA[2]LEN)/European Dermatology Forum (EDF)/World Allergy Organization (WAO) [2018] define chronic urticaria as urticaria that has been continuously or intermittently present for at least 6 weeks.[18,19] Continuous therapy with antihistamines (second generation H1-antagonists) is generally recommended as first-line pharmacologic treatment for urticaria following trigger avoidance. If symptoms persist following 2 to 4 weeks of initial therapy, the dose of the second generation H1-antagonist should be increased to up to 4-fold. For patients with refractory chronic urticaria, the addition of Xolair may be considered.

Nasal Polyp Guidelines

A 2014 Practice Parameter on the Diagnosis and Management of Rhinosinusitis and a 2020 Practice Parameter for the Management of Rhinitis from the JTFPP recommend nasal corticosteroids be used in patients with chronic rhinosinusitis with nasal polyps, as they decrease nasal polyp size, prevent regrowth of nasal polyps following surgical removal, and improve nasal symptoms.[20-23] Short courses of oral corticosteroids are also recommended. Endoscopic surgical intervention may be considered as an adjunct to medical therapy in patients with chronic rhinosinusitis that is not responsive or is poorly responsive to medical therapy. The parameter lists Xolair as a therapy that may be considered for the treatment of nasal polyps based on the limited data available at the time of publication. A 2015 Clinical Practice Guideline update on Adult Sinusitis from the American Academy of Otolaryngology (AAO) makes similar recommendations, stating that clinicians should recommend saline nasal irrigation, topical nasal corticosteroids, or both for symptom relief in patients with chronic rhinosinusitis (with or without nasal polyps).[24] The AAO guidelines do not address Xolair.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Xolair. All approvals are provided for the duration noted below. In cases where approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Xolair, as well as the monitoring required for adverse events and long-term efficacy, approval requires Xolair to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xolair is recommended in those who meet one of the following criteria:

FDA-Approved Indications

18. Asthma. Approve Xolair for the duration noted if the patient meets one of the following conditions (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets the following criteria (i, ii, iii, iv, v, and vi):

i. Patient is ≥ 6 years of age; AND

ii. Patient has a baseline immunoglobulin E (IgE) level ≥ 30 IU/mL; AND
Note: "Baseline" is defined as prior to receiving any Xolair or anti-interleukin 4/13 therapy (i.e., Dupixent® [dupilumab subcutaneous injection]).

iii. Patient has a baseline positive skin test or *in vitro* test (i.e., a blood test) for allergen-specific immunoglobulin E (IgE) for one or more perennial aeroallergens and/or for one or more seasonal aeroallergens; AND
Note: "Baseline" is defined as prior to receiving any Xolair or anti-interleukin 4/13 therapy (i.e. Dupixent). Examples of perennial aeroallergens are house dust mite, animal dander, cockroach, feathers, and mold spores. Examples of seasonal aeroallergens are grass, pollen, and weeds.

iv. Patient has received at least 3 consecutive months of combination therapy with BOTH of the following (a and b):

a) An inhaled corticosteroid; AND

b) At least one additional asthma controller or asthma maintenance medication; AND
Note: Examples of additional asthma controller or asthma maintenance medications are inhaled long-acting beta$_2$-agonists, inhaled long-acting muscarinic antagonists, leukotriene receptor antagonists, Dupixent® (dupilumab subcutaneous injection), and theophylline. Use of a combination inhaler containing both an inhaled corticosteroid and additional asthma controller/maintenance medication(s) would fulfil the requirement for both criteria a and b.

v. Patient has asthma that is uncontrolled or was uncontrolled at baseline as defined by ONE of the following (a, b, c, d, or e):

a) Patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR

b) Patient experienced one or more asthma exacerbation(s) requiring hospitalization or an Emergency Department visit in the previous year; OR

c) Patient has a forced expiratory volume in 1 second (FEV_1) < 80% predicted; OR

d) Patient has an FEV_1/forced vital capacity (FVC) < 0.80; OR

e) Patient has asthma that worsens upon tapering of oral corticosteroid therapy; AND
Note: "Baseline" is defined as prior to receiving any Xolair or anti-interleukin 4/13 therapy (i.e. Dupixent® [dupilumab subcutaneous injection]).

vi. The medication is prescribed by or in consultation with an allergist, immunologist, or pulmonologist.

B) Patient is Currently Receiving Xolair. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):

i. Patient has already received at least 4 months of therapy with Xolair; AND
Note: A patient who has received < 4 months of therapy or who is restarting therapy with Xolair should be considered under criterion 1A (Asthma, Initial Therapy).

ii. Patient continues to receive therapy with one inhaled corticosteroid or one inhaled corticosteroid-containing combination inhaler; AND

iii. Patient has responded to therapy as determined by the prescriber.

Note: Examples of a response to Xolair therapy are decreased asthma exacerbations; decreased asthma symptoms; decreased hospitalizations, emergency department/urgent care, or medical clinic visits due to asthma; decreased reliever/rescue medication use; and improved lung function parameters.

19. Chronic Idiopathic Urticaria (Chronic Spontaneous Urticaria). Approve Xolair for the duration noted if the patient meets one of the following conditions (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets the following criteria (i, ii, and iii):

i. Patient is ≥ 12 years of age; AND

ii. Patient has/had urticaria for > 6 weeks (prior to treatment with Xolair), with symptoms present > 3 days per week despite daily non-sedating H_1 antihistamine therapy with doses that have been titrated up to a maximum of four times the standard FDA-approved dose; AND

Note: Examples of non-sedating H_1 antihistamine therapy are cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine.

iii. The medication is prescribed by, or in consultation with an allergist, immunologist, or dermatologist.

B) Patient is Currently Receiving Xolair. Approve Xolair for 1 year if the patient meets the following criteria (i and ii):

i. Patient has already received at least 4 months of therapy with Xolair; AND

Note: A patient who has received < 4 months of therapy or who is restarting therapy with Xolair should be considered under criterion 2A (Chronic Idiopathic Urticaria, Initial Therapy).

ii. Patient has responded to therapy as determined by the prescriber.

Note: Examples of a response to Xolair therapy are decreased severity of itching, decreased number and/or size of hives.

20. Nasal Polyps. Approve Xolair for the duration noted if the patient meets one of the following conditions (A or B):

21. Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv, v, and vi):

22. Patient is ≥ 18 years of age; AND

23. Patient has a baseline immunoglobulin E (IgE) level ≥ 30 IU/mL; AND
Note: "Baseline" is defined as prior to receiving any Xolair or anti-interleukin 4/13 therapy (i.e., Dupixent® [dupilumab subcutaneous injection]).

24. Patient is experiencing significant rhinosinusitis symptoms such as nasal obstruction, rhinorrhea, or reduction/loss of smell according to the prescriber; AND

25. Patient is currently receiving therapy with an intranasal corticosteroid; AND

26. Patient meets ONE of the following (a or b):

27. Patient has received treatment with a systemic corticosteroid for chronic rhinosinusitis with nasal polyps within the previous 2 years or has a contraindication to systemic corticosteroid therapy; OR

28. Patient has had prior surgery for nasal polyps; AND

29. The medication is prescribed by or in consultation with an allergist, immunologist, or an otolaryngologist (ear, nose and throat [ENT] physician specialist).

30. Patient is currently receiving Xolair. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):

31. Patient has already received at least 6 months of therapy with Xolair; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with Xolair should be considered under criterion 3A (Nasal Polyps, Initial Therapy).

32. Patient continues to receive therapy with an intranasal corticosteroid; AND

33. Patient has responded to Xolair therapy as determined by the prescriber.
Note: Examples of a response to Xolair therapy are reduced nasal polyp size, improved nasal congestion, reduced sinus opacification, decreased sino-nasal symptoms, and/or improved sense of smell.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xolair is not recommended in the following situations:

1. Atopic Dermatitis. One single-center, double-blind, placebo-controlled trial, Atopic Dermatitis Anti-IgE Pediatric Trial (ADAPT) evaluated the efficacy of Xolair in patients 4 to 19 years of age with severe atopic dermatitis (n = 62).[25] After 24 weeks of therapy, the difference in the objective Scoring Atopic Dermatitis [SCORAD] index with Xolair vs. placebo was -6.9 (P = 0.01). This was statistically significant; however, the clinical significance is unknown. Quality of life measurements were also improved with Xolair. Smaller studies have not shown benefit and case studies have yielded mixed results.[25-27] Additional larger, well-designed clinical trials are needed to determine if Xolair has a role in the treatment of atopic dermatitis. Atopic dermatitis guidelines from the American Academy Dermatology (AAD) [2014] note that data are limited to determine if Xolair is efficacious.[28] These guidelines do not make a recommendation regarding Xolair use in this patient population. European consensus guidelines for the treatment of atopic dermatitis (2018) also note the mixed data and state that they cannot recommend Xolair for the treatment of atopic dermatitis.[29]

2. Concurrent use of Xolair with an Anti-Interleukin (IL) Monoclonal Antibody. The efficacy and safety of Xolair used in combination with IL antagonist monoclonal antibodies (e.g., Cinqair® [reslizumab injection for intravenous use], Fasenra™ [benralizumab injection for subcutaneous use], Nucala® [mepolizumab injection for subcutaneous use], Dupixent® [dupilumab subcutaneous injection]) have not been established. There are very limited case reports describing the combined use of Nucala and Xolair for severe asthma as well as off-label indications.[30-32] Further investigation is warranted.

3. Eosinophilic Gastroenteritis, Eosinophilic Esophagitis, or Eosinophilic Colitis. There are limited and conflicting data from very small studies and case series on the use of Xolair for the treatment of eosinophilic gastrointestinal conditions.[33-36] Guidelines for the management of eosinophilic esophagitis from the American Gastroenterological Association (AGA) and the Joint Task Force on Allergy-Immunology Practice Parameters (2020) recommend against the use of Xolair in patients with this condition.[37]

4. **Latex Allergy in Health Care Workers with Occupational Latex Allergy.** A small European study assessed the effects of Xolair treatment in health care workers (n = 18) with occupational latex allergy.[38] Xolair use in these patients resulted in a reduction in mean conjunctival challenge test scores as compared with placebo-treated patients after 16-weeks of therapy. Also, three patients who did not respond to Xolair treatment during the double-blind phase responded during the 16-week open-label phase. Thus the overall ocular response rate for all patients in the open-label phase was 93.8% (n = 15/16). Also 11 of 15 patients in the open-label phase had a negative response to a latex glove challenge test (4 patients had a mild response). Well-controlled trials are needed.

5. **Peanut and Other Food Allergies.** Limited data are available regarding the use of Xolair to facilitate desensitization to food allergens. A Phase II multicenter clinical trial was initiated using Xolair in patients with peanut allergy; however, it was discontinued prematurely due to concerns regarding the safety of the oral peanut challenges in some patients.[39] Insufficient data were obtained to reach any conclusions about the efficacy of Xolair. Data are also available from a small pilot study examining the use of Xolair to facilitate rapid oral desensitization in high-risk peanut-allergic patients.[40] There are also minimal data (a Phase I study and a case series) on the use of Xolair to facilitate desensitization in patients with severe cow's milk allergy.[41-44] Additionally, a Phase I study and a Phase II study have evaluated the use of Xolair to facilitate desensitization in patients with multiple food allergies.[45,46] Guidelines for the diagnosis and management of food allergy in the US from the National Institute of Allergy and Infectious Diseases (NIAID) [2010] indicate there are currently no medications recommended to prevent IgE-mediated or non-IgE-mediated food-induced allergic reactions from occurring in an individual with existing food allergies.[47] The Practice Parameter on Food Allergy from the Joint Task Force on Practice Parameters (JTFPP), representing the American Academy of Allergy, Asthma, & Immunology (AAAAI); the American College of Allergy, Asthma, & Immunology (ACAAI); and the Joint Council of Allergy, Asthma, & Immunology (JCAAI) [2014] also states that immunotherapies (such as the oral immunotherapy desensitization described above) show promise for the treatment of food allergy; however, there is currently inadequate evidence that the therapeutic benefit outweighs the risk.[48] Trials of these have been uncontrolled, small studies, which are subject to selection bias and uncertain safety profiles. However, treatment with anti-IgE monoclonal antibodies might increase the threshold for doses needed to stimulate an allergic reaction and potentially may enhance the safety profile for patients. Additional well-controlled trials are needed.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	• Updated initial therapy criteria for "Asthma in Patients with Moderate to Severe Persistent Disease" to state that the baseline IgE level ≥ 30 IU/mL should be prior to treatment with Xolair or anti-IL-4/13 therapy (Dupixent). Previously criteria only noted the level should be prior to Xolair therapy. • Updated initial therapy criteria for "Asthma in Patients with Moderate to Severe Persistent Disease" to more concisely state the previous therapies required. Added the following note: An exception to the requirement for a trial of one additional asthma controller/maintenance medication (criterion b) can be made if the patient has already received anti-IL-4/13 therapy (Dupixent) used concomitantly with an ICS for at least 3 consecutive months. • Updated initial therapy criteria for "Asthma in Patients with Moderate to Severe Persistent Disease" to state that the patient's asthma is uncontrolled or was uncontrolled prior to receiving any Xolair or anti-IL-4/13 therapy (Dupixent). Previously criteria only stated it should be uncontrolled prior to Xolair therapy.	01/23/2019
Annual Revision	• **Asthma**: Approval indication was changed from "Asthma in Patients with Moderate to Severe Persistent Disease" to "Asthma". Removed examples of *in vitro* allergen-specific IgE tests: ELISA (ImmunoCAP™) or RAST. Wording in reference to "according to the prescribing physician" was changed to "according to the prescriber". Removed lists of examples of inhaled asthma controller/maintenance medications. • **Chronic Idiopathic Urticaria**: Wording in reference to "according to the prescribing physician" was changed to "according to the prescriber". • **Allergic Rhinitis**: Approval indication was changed from "Allergic Rhinitis, Seasonal or Perennial" to "Allergic Rhinitis". Updated requirement that patient have a positive skin test or in vitro test for allergen-specific IgE for "one or more relevant allergens" to "one or more perennial aeroallergens AND/OR for one or more seasonal aeroallergens" (previously criteria listed both perennial and aeroallergen examples as relevant allergens, updated wording to be consistent with Asthma approval criteria). Wording in reference to "second-generation/less-sedating antihistamines" was changed to "non-sedating H_1 antihistamines". Wording in reference to "according to the prescribing physician" was changed to "according to the prescriber". Removed lists of examples of intranasal antihistamines and intranasal corticosteroids.	02/12/2020
Selected Revision	• Removed Allergic Rhinitis as an "Other Use with Supported Evidence"	03/25/2020
Selected Revision	• **Nasal Polyps**: Added new approval criteria for this indication which include an age requirement, a minimum IgE level at baseline, the presence of significant rhinosinusitis symptoms, current intranasal corticosteroid therapy, previous systemic therapy (or contraindication) or surgery for nasal polyps, and involvement of a specialist.	12/16/2020
Annual Revision	No criteria changes.	02/17/2021

IgE – Immunoglobulin E; IL – Interleukin; ICS – Inhaled corticosteroids; ELISA – Enzyme-linked immunoabsorbant assay; RAST – Radioallergosorbent test.

PRIOR AUTHORIZATION POLICY

POLICY: Infectious Disease – Daraprim Prior Authorization Policy

- Daraprim® (pyrimethamine tablets – Vyera Pharmaceuticals)

REVIEW DATE: 10/28/2020

OVERVIEW

Daraprim is indicated for the treatment of **toxoplasmosis** when used conjointly with a sulfonamide, since synergism exists with this combination.[1]

Toxoplasmosis is an infection caused by the protozoan parasite, *Toxoplasma gondii*.[2] In the US, it is estimated that 11% of the population ≥ 6 years of age have been infected with *Toxoplasma*. The incidence is > 60% in some areas of the world. The parasite can be transmitted by food (e.g., by eating undercooked, contaminated meat or shellfish), through infected cats (cats become infected by eating infected rodents, birds, or other small animals), or by mother-to-child (congenital) transmission.

Pyrimethamine, a folic acid antagonist, is considered to be the most effective drug against toxoplasmosis and is a standard component of therapy.[2] Leucovorin, a folinic acid, protects the bone marrow from the toxic effects of pyrimethamine and is often prescribed in conjunction with pyrimethamine.

Guidelines

The guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with human immunodeficiency (HIV) [2020] recommend pyrimethamine as the drug of choice for treatment and chronic maintenance treatment (secondary prophylaxis) of *Toxoplasma gondii* encephalitis.[3] Pyrimethamine is recommended as an option for: primary prophylaxis of *Toxoplasma gondii* encephalitis; primary prophylaxis and chronic maintenance treatment (secondary prophylaxis) of *Pneumocystis* pneumonia; and chronic maintenance treatment (secondary prophylaxis) and treatment of cystoisosporiasis (formerly isosporiasis).[3] The drug of choice for these conditions is trimethoprim-sulfamethoxazole.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Daraprim. All approvals are provided for 1 year in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Daraprim is recommended in those who meet one of the following criteria:

FDA-Approved Indications

20. Treatment of Toxoplasmosis. Approve for 1 year.

Other Uses with Supportive Evidence

21. **Cystoisosporiasis (formerly known as isosporiasis) – Chronic Maintenance Treatment (Secondary Prophylaxis).** Approve for 1 year if the patient has tried one other therapy for this condition.
    Note: Other therapies used for this condition include trimethoprim-sulfamethoxazole and ciprofloxacin.

22. **Cystoisosporiasis (formerly known as isosporiasis) – Treatment.** Approve for 1 year if the patient has tried one other therapy for this condition.
    Note: Other therapies used for this condition include trimethoprim-sulfamethoxazole and ciprofloxacin.

~~23.~~ ***Pneumocystis*** **Pneumonia – Chronic Maintenance Therapy (Secondary Prophylaxis).** Approve for 1 year if the patient has tried one other therapy for this condition.
Note: Other therapies used for this condition include trimethoprim-sulfamethoxazole, dapsone, aerosolized pentamidine (via Respirgard II™ nebulizer), and atovaquone.

~~24.~~ ***Pneumocystis*** **Pneumonia – Primary Prophylaxis.** Approve for 1 year if the patient has tried one other therapy for this condition.
Note: Other therapies used for this condition include trimethoprim-sulfamethoxazole, dapsone, aerosolized pentamidine (via Respirgard II™ nebulizer), and atovaquone.

~~25.~~ ***Toxoplasma gondii*** **Encephalitis – Chronic Maintenance Therapy (Secondary Prophylaxis).** Approve for 1 year.

~~26.~~ ***Toxoplasma gondii*** **Encephalitis – Primary Prophylaxis.** Approve for 1 year if the patient has tried one other therapy for this condition.
Note: Other therapies used for this condition include trimethoprim-sulfamethoxazole and atovaquone.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Daraprim is not recommended in the following situations:

7. **Malaria – Chemoprophylaxis or Treatment.** Daraprim is no longer indicated for the treatment of acute malaria or for chemoprophylaxis of malaria.[1] Even when malaria was an approved indication, the Centers for Disease Control and Prevention (CDC) did not include Daraprim as a recommended therapy for malaria (due to widespread resistance).

8. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/02/2019
Annual Revision	• **Cystoisosporiasis (formerly known as isosporiasis) – Chronic Maintenance Treatment (Secondary Prophylaxis):** Deleted option for approval for patients who have contraindications to other therapies. Examples of treatment options were added as a Note. • **Cystoisosporiasis (formerly known as isosporiasis) – Treatment:** Deleted option for approval for patients who have contraindications to other therapies. Examples of treatment options were added as a Note. • ***Pneumocystis* Pneumonia – Chronic Maintenance Therapy (Secondary Prophylaxis):** Deleted option for approval for patients who have contraindications to other therapies. Examples of treatment options were added as a Note. • ***Pneumocystis* Pneumonia – Primary Prophylaxis:** Deleted option for approval for patients who have contraindications to other therapies. Examples of treatment options were added as a Note. • ***Toxoplasma gondii* Encephalitis – Chronic Maintenance Therapy (Secondary Prophylaxis):** Deleted criterion "Approve for 1 year if the patient has tried one other therapy for this condition or has contraindications to that therapy". • ***Toxoplasma gondii* Encephalitis – Primary Prophylaxis:** Deleted option for approval for patients who have contraindications to other therapies. Examples of treatment options were added as a Note.	10/28/2020

PRIOR AUTHORIZATION POLICY

POLICY: Infectious Disease – Pretomanid Prior Authorization Policy

- Pretomanid tablets (Global Alliance for TB Drug Development/Mylan Laboratories)

REVIEW DATE: 10/21/2020

OVERVIEW

Pretomanid, a nitroimidazole, is indicated as part of a combination regimen with Sirturo® (bedaquiline tablets) and linezolid tablets or oral suspension (Zyvox®, generics) for the treatment of adults with pulmonary extensively drug resistant (XDR) or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB).[1] Limitation of use: Pretomanid is not indicated for use in patients with the following conditions: drug-sensitive TB, latent infections due to *Mycobacterium tuberculosis*, extra-pulmonary infection due to *M. tuberculosis*, MDR-TB that is not treatment-intolerant or nonresponsive to standard therapy. The safety and effectiveness of Pretomanid when used with drugs other than Sirturo and linezolid have not been established.

The prescribing information notes the total duration of treatment with Pretomanid to be 26 weeks.[1] The World Health Organization (WHO) Global Tuberculosis Report 2020 notes that treatment ranges from 6 to

20 months for MDR-TB or rifampicin-resistant TB (RR-TB) and possibly longer if there is additional drug resistance or if clinical and laboratory outcomes at the end of treatment are unsatisfactory.[2]

Globally, drug-resistant TB is a public health crisis.[2] In 2019, close to half a million people developed RR-TB. Of these cases, 78% were MDR-TB. Overall, 3.3% of new TB cases and 17.7% of previously treated cases were MDR/RR-TB. The global treatment success rate for MDR/RR-TB is 57%.

Guidelines

Pretomanid has not been added to the WHO consolidated guidelines for the treatment of drug-resistant TB (including MDR-TB and RR-TB) [2019]; these guidelines were consolidated from eight previously issued WHO guideline documents.[3] Treatment of MDR/RR-TB should be started with at least four TB drugs that are likely to be effective. It is recommended that the regimen be comprised of either levofloxacin or moxifloxacin, Sirturo, linezolid, and one of: clofazimine (only available through a single-person treatment investigational new drug protocol through the FDA), cycloserine, or terizidone. If these drugs cannot be used, the following drugs can be selected: ethambutol, delamanid (available through a compassionate use program), pyrazinamide, imipenem-cilastatin or meropenem, amikacin or streptomycin, Trecator® (ethionamide) or prothionamide (not available in the US), or Paser® (p-aminosalicyclic acid).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Pretomanid. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Pretomanid as well as monitoring required for adverse events and long-term efficacy, approval requires Pretomanid to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Pretomanid is recommended in those who meet the following criteria:

FDA-Approved Indications

34. Tuberculosis, Pulmonary Extensively Drug Resistant or Treatment-Intolerant or Nonresponsive Multidrug-Resistant. Approve for 9 months if the patient meets the following criteria (A, B, and C):
- **C)** Patient is ≥ 18 years of age; AND
- **D)** Pretomanid is prescribed in combination with Sirturo® (bedaquiline tablets) and linezolid tablets or oral suspension (Zyvox®, generics); AND
- **E)** The medication is prescribed by or in consultation with an infectious diseases specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Pretomanid is not recommended in the following situations:

9. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/16/2019
Annual Revision	No criteria changes.	10/21/2020

PRIOR AUTHORIZATION POLICY

POLICY: Infectious Disease – Sirturo® Prior Authorization Policy

- Sirturo® (bedaquiline fumarate tablets – Janssen Therapeutics, Division of Janssen Products LP)

REVIEW DATE: 10/21/2020

OVERVIEW

Sirturo, a diarylquinolone antimycobacterial, is indicated as part of a combination therapy in the treatment of adult and pediatric patients (≥ 5 years and weighing ≥ 15 kg) with pulmonary multidrug-resistant tuberculosis (MDR-TB).[1] Sirturo should be used when an effective treatment regimen cannot otherwise be provided. Limitations of use: Sirturo should not be used for latent infections due to *Mycobacterium tuberculosis*, drug-sensitive tuberculosis (TB), extra-pulmonary TB, and infections caused by non-tuberculous mycobacteria. The safety and efficacy of Sirturo in the treatment of patients infected with human immunodeficiency virus (HIV) with MDR-TB have not been established as clinical data are limited.

Sirturo should be used in combination with at least three other drugs to which the patient's MDR-TB isolate has been shown to be susceptible *in vitro*.[1] If *in vitro* testing results are not available, Sirturo may be initiated in combination with at least four other drugs to which the patient's MDR-TB isolate is likely to be susceptible.

The prescribing information notes the total duration of treatment with Sirturo to be 24 weeks (adults and pediatric patients).[1] However, the World Health Organization (WHO) Global Tuberculosis Report 2020 notes that treatment ranges from 6 to 20 months for MDR-TB or rifampicin-resistant TB (RR-TB) and possibly longer if there is additional drug resistance or if clinical and laboratory outcomes at the end of treatment are unsatisfactory.[2]

Globally, drug-resistant TB is a public health crisis.[2] In 2019, close to half a million people developed RR-TB. Of these cases, 78% were MDR-TB. Overall, 3.3% of new TB cases and 17.7% of previously treated cases were MDR/RR-TB. The global treatment success rate for MDR/RR-TB is 57%.

Guidelines

The WHO issued consolidated guidelines for the treatment of drug-resistant TB (including MDR-TB and RR-TB) in 2019; these guidelines were consolidated from eight previously issued WHO guideline documents.[3] Treatment of MDR/RR-TB should be started with at least four TB drugs that are likely to be effective. It is recommended that the regimen be comprised of either levofloxacin or moxifloxacin, Sirturo,

linezolid, and one of: clofazimine (only available through a single-person treatment investigational new drug protocol through the FDA), cycloserine, or terizidone. If these drugs cannot be used, the following drugs can be selected: ethambutol, delamanid (available through a compassionate use program), pyrazinamide, imipenem-cilastatin or meropenem, amikacin or streptomycin, Trecator® (ethionamide) or prothionamide (not available in the US), or Paser® (p-aminosalicyclic acid).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Sirturo. All approvals are provided for the duration noted below. In cases where approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Sirturo as well as monitoring required for adverse events and long-term efficacy, approval requires Sirturo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sirturo is recommended in those who meet the following criteria:

FDA-Approved Indications

35. Tuberculosis, Pulmonary Multidrug-Resistant or Extensively Drug-Resistant. Approve for 9 months if the patient meets the following criteria (A, B, C, and D):

- **F)** Patient is ≥ 5 years of age; AND
- **G)** Patient weighs ≥ 15 kg; AND
- **H)** Sirturo is prescribed as part of a combination regimen with other anti-tuberculosis agents; AND
- **I)** The medication is prescribed by or in consultation with an infectious diseases specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sirturo is not recommended in the following situations:

10. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/16/2019
Annual Revision	**Tuberculosis, Pulmonary Multidrug-Resistant or Extensively Drug-Resistant:** age requirement was changed to ≥ 5 years of age and weight requirement was changed to ≥ 15 kg, per the updated prescribing information.	10/21/2020

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Actemra® (tocilizumab for intravenous infusion – Genentech/Roche)

DATE REVIEWED: 03/25/2020

OVERVIEW

Actemra for intravenous (IV) injection is a recombinant humanized interleukin-6 (IL-6) receptor inhibitor indicated for the following conditions:[1]

1. cytokine release syndrome, in patients ≥ 2 years of age with severe or life-threatening disease associated with chimeric antigen receptor (CAR) T-cell therapy; AND
2. Polyarticular juvenile idiopathic arthritis (PJIA), for the treatment of active in patients 2 years of age and older; AND
3. Rheumatoid arthritis (RA), for treatment of adults with moderate to severe active disease who have had an inadequate response to one or more disease modifying antirheumatic drugs (DMARDs); AND
4. Systemic juvenile idiopathic arthritis (SJIA), for the treatment of active disease in patients two years of age and older.

Actemra IV has been shown to inhibit and slow structural joint damage, improve physical function, and achieve a major clinical response in patients taking methotrexate (MTX). In RA, Actemra IV can be given alone or in combination with other nonbiologic DMARDs. For PJIA and SJIA, Actemra IV can be given alone or in combination with MTX. Actemra is also available as a subcutaneous (SC) formulation which, in addition to RA, is indicated for giant cell arteritis (GCA).

Disease Overview

Targeting IL-6 is a therapeutic option for treatment of chronic inflammatory diseases such as RA.[2] IL-6 has been shown to be involved in diverse physiological processes and is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as RA. Actemra is an IL-6 receptor monoclonal antibody that binds to soluble and membrane-bound IL-6 receptors and has been shown to inhibit IL-6-mediated signaling through these receptors.[1] In CRS (reported in 79% to 94% of patients receiving CAR T-cell therapy), there are high levels of IL-6; therefore, IL-6 signaling is inhibited with Actemra IV.[1,3-5]

Guidelines

Il-6 blockers are mentioned in multiple guidelines for treatment of inflammatory conditions.

- Cytokine Release Syndrome: The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for Management of Immunotherapy-Related Toxicities (version 1.2020 – December 16, 2019) give specific recommendations for use of Actemra in the management of inflammatory arthritis, cytokine release syndrome, and CAR T-cell-related toxicities.[6]
    - For immune checkpoint inhibitor-related inflammatory arthritis, infliximab or Actemra may be considered for refractory or severe arthritis not responding to steroids and anti-inflammatory agents.
- PJIA: The American College of Rheumatology (ACR)/Arthritis Foundation guidelines for the treatment of JIA (2019) specific to juvenile non-systemic polyarthritis, sacroiliitis, and enthesitis.[7] For patients without risk factors, initial therapy with a DMARD is conditionally recommended over a biologic (including Actemra). Biologics (e.g., Actemra) are conditionally recommended as initial treatment when combined with a DMARD over biologic monotherapy.
- RA: Guidelines from the ACR (2015) for the treatment of rheumatoid arthritis have tumor necrosis factor (TNF) inhibitors and non-TNF biologics (such as Actemra) equally positioned as a recommended therapy following a trial of a conventional synthetic DMARD (e.g., MTX, leflunomide, hydroxychloroquine, sulfasalazine).[9]
- SJIA: The 2013 update of the 2011 ACR recommendations for the treatment of SJIA mention Actemra as a second- or third-line agent in patients with active systemic features and varying degrees of synovitis and in patients without active systemic features and varying degrees of

synovitis.[8] Nonsteroidal anti-inflammatory drugs NSAIDs, systemic glucocorticoids, Kineret, TNF inhibitors, and MTX are among other treatment options.

- Castleman's Disease: The NCCN clinical practice guidelines for B-cell Lymphomas (version 1.2020 – January 22, 2020) mention Actemra as a second-line therapy for relapsed or refractory unicentric Castleman's disease in patients who are HIV- and HHV-8-negative.[10] For multicentric Castleman's disease (MCD), the guidelines list Actemra as a subsequent therapy for relapsed, refractory, or progressive MCD.

Other Uses With Supportive Evidence

Still's disease presents in adults with features similar to those of SJIA.[11] Actemra IV has been effective in reducing fever, symptoms, and markers of inflammation in patients who were refractory to treatment with prednisone, MTX, Kineret, and/or a TNF antagonist.[11-20] Prospective, randomized, controlled trials are needed.

COVID-19 (Coronavirus Disease 2019)

COVID-19 is a novel coronavirus that has not previously been identified and with no approved treatments.[24] COVID-19 can cause mild to severe illness, including symptoms of fever, cough, shortness of breath, myalgia, and/or fatigue. In COVID-19, the body may respond to the virus by overproducing immune cells and their signaling molecules in a phenomenon called cytokine release storm.[25] By inhibiting IL-6, Actemra is speculated to associated with better clinical outcomes, such as decreased systemic inflammation, improved survival rate, better hemodynamic and improved of respiratory distress. Clinical trials are underway evaluating Actemra in patients with severe or critical cytokine release syndrome.

In a retrospective analysis from China, 21 patients with severe or critical COVID-19 were treated with Actemra IV (18 patients received one dose [400 mg IV] and 3 patients received a second dose within 12 hours).[26] All patients had a 1-week history of routine treatment prior to Actemra. All patients received standard therapy, including lopinavir, methylprednisolone, other symptom relievers, and oxygen therapy. The mean age of enrolled patients was 57 years (range 25 to 88 years), and the majority (n = 18/21) were male. Overall, 17 patients were categorized with severe disease (defined as respiratory rate $\geq$ 30 breaths/min, peripheral oxygen saturation [SpO2] $\leq$ 93% [room air], and/or partial pressure of arterial oxygen/percentage of inspired oxygen [PaO2/FiO2] $\leq$ 300 mmHg). There were also four patients categorized as critical (defined as respiratory failure requiring mechanical ventilation; shock; or intensive care unit admission combined with other organ failure). All patients had abnormal computed tomography (CT) of the chest, primarily with plaque-like, ground-glass opacities and focal consolidation, mainly distributed in the peripheral (especially the subpleural) region. Mean IL-6 expression levels (132.38 ± 278.54 pg/ml) prior to administration of Actemra suggested upregulation of IL-6. Body temperature of all patients normalized on the first day after receiving Actemra and remained stable thereafter. After treatment, CT scans showed that the chest lesions were absorbed in 19 patients (90.5%). At the time this analysis was published, 19 patients (90.5%) were discharged (average of 13.5 days after the treatment with Actemra) and the remaining patients continued to recover. There have been no reports of subsequent pulmonary infection, deterioration of illness, or death.

Safety

Actemra has boxed warnings concerning risks of serious infection.[1] Prior to initiating therapy, patients should be evaluated for active tuberculosis (TB) infection, and periodically during therapy patients should be assessed for latent TB infection. If a serious infection develops, treatment with Actemra should be interrupted until infection is controlled. The prescribing information for Kymriah and Yescarta have Boxed Warnings regarding CRS that may be severe or life-threatening.[3-4] Both have a Risk Evaluation and Mitigation Strategy (REMS) which requires at least two doses of Actemra on hand prior to infusion and during the recovery process.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Actemra IV. Because of the specialized skills required for evaluation and diagnosis of patients treated with Actemra IV as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Actemra IV to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration listed below. When approvals are authorized in months, 1 month is equal to 30 days. When authorized in weeks, 1 week is equal to 7 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Actemra IV is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Cytokine Release Syndrome (CRS) Associated with Chimeric Antigen Receptor (CAR) T-Cell Therapy.** Approve Actemra IV for 1 week (which is adequate duration to receive 4 doses) if prescribed for a patient who has been or will be treated with a chimeric antigen receptor (CAR) T-cell therapy.
   Note: Examples of CAR T-cell therapy include Kymriah™ (tisagenlecleucel IV suspension) and Yescarta™ (axicabtagene ciloleucel IV suspension). If the patient has **CRS due to COVID-19** (coronavirus disease 2019) refer to the criteria for Other Uses With Supportive Evidence (below).

2. **Polyarticular Juvenile Idiopathic Arthritis (PJIA).** Approve for the duration noted if the patient meets ONE of the following (A or B):
   A) Initial Therapy. Approve for 4 months if the patient meets BOTH of the following criteria (i and ii):
      i. The patient meets one of the following conditions (a, b, c, or d):
         a) The patient has tried one other agent for this condition.
         Note: Examples of one other agent tried include methotrexate (MTX), sulfasalazine, leflunomide, or a nonsteroidal anti-inflammatory drug (NSAID). A biologic (refer to **Appendix** for examples of biologics used for PJIA) also counts as a trial of one agent for PJIA; OR
         b) The patient will be starting on Actemra IV concurrently with methotrexate (MTX), sulfasalazine, or leflunomide; OR
         c) The patient has an absolute contraindication to methotrexate (MTX), sulfasalazine, or leflunomide; OR
         Note: Examples of absolute contraindication to methotrexate include pregnancy, breast feeding, alcoholic liver disease, immunodeficiency syndrome, and blood dyscrasias.
         d) The patient has aggressive disease, as determined by the prescriber; AND
      ii. The agent is prescribed by or in consultation with a rheumatologist.
   B) Patients Currently Receiving Actemra (IV or SC). Approve for 1 year if the patient has had a response, as determined by the prescriber.
   Note: Examples of response include improvement in limitation of motion; less joint pain or tenderness; improved function or activities of daily living; decreased duration of morning stiffness or fatigue; reduced dosage of corticosteroids; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values. The patient may not have a full response, but there should have been a recent or past response to Actemra IV or SC.

3. **Rheumatoid Arthritis (RA).** Approve for the duration noted if the patient meets ONE of the following (A or B):
   A) Initial Therapy. Approve for 3 months if the patient meets the following criteria (i and ii):

i. The patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months.
Note: Examples of one conventional DMARD tried include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already had a 3-month trial of at least one biologic (refer to **Appendix** for examples of biologics used for RA). These patients who have already tried a biologic for RA are not required to "step back" and try a conventional synthetic DMARD; AND

ii. The agent is prescribed by or in consultation with a rheumatologist.

B) Patients Currently Receiving Actemra (IV or SC). Approve for 1 year if the patient has had a response, as determined by the prescriber.
Note: Examples of response include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Actemra IV or SC.

4. Systemic Juvenile Idiopathic Arthritis (SJIA). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following criteria (i and ii):

i. The patient has tried one other systemic agent for this condition.
Note: Examples of one other systemic agent tried include a corticosteroid (oral, IV), a conventional synthetic disease-modifying antirheumatic drug (DMARD) [e.g., methotrexate {MTX}, leflunomide, sulfasalazine], or a 1-month trial of a nonsteroidal anti-inflammatory drug (NSAID). A previous trial of a biologic such as Kineret (anakinra SC injection), a tumor necrosis factor (TNF) inhibitor (e.g., an etanercept product, an adalimumab product, or an infliximb product, or Ilaris [canakinumab for SC injection]) also counts towards a trial of one other systemic agent for SJIA; AND

ii. The agent is prescribed by or in consultation with a rheumatologist.

B) Patients Currently Receiving Actemra (IV or SC). Approve for 1 year if the patient has had a response, as determined by the prescriber.
Note: Examples of response include improvement in limitation of motion; less joint pain or tenderness; decreased duration of morning stiffness or fatigue; improved function or activities of daily living; reduced dosage of corticosteroids; less joint pain or tenderness; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values. The patient may not have a full response, but there should have been a recent or past response to Actemra IV or SC.

Other Uses with Supportive Evidence

5. Castleman's Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 4 months if the agent is prescribed by or in consultation with an oncologist or hematologist; OR

B) Patients Currently Receiving Actemra (IV or SC). Approve for 1 year if the patient has responded, as determined by the prescriber.
Note: Examples of response include normalization of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, albumin, and hemoglobin; resolution of constitutional symptoms; increased body mass index (BMI), and reduction in lymphadenopathy.

6. COVID-19 (Coronavirus Disease 2019). Approve for 1 week if, according to the prescriber, the patient has cytokine release syndrome associated with COVID-19.

Note: Denials for patients diagnosed with COVID-19 are forwarded to the Medical Director.

7. **Inflammatory Arthritis Associated with Checkpoint Inhibitor Therapy.** Approve for 3 months if the patient meets ONE of the following (A or B):
   Note: Examples of checkpoint inhibitors include Keytruda (pembrolizumab IV infusion), Opdivo (nivolumab IV infusion), Yervoy (ipilimumab IV infusion), Tecentriq (atezolizumab IV infusion), Bavencio (avelumab IV infusion), Imfinzi (durvalumab IV infusion), and Libtayo® (cemiplimab-rwlc IV infusion).
   A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, and iii):
      i. The patient is symptomatic despite a trial of at least ONE systemic corticosteroid.
      Note: Examples of a systemic corticosteroid include methylprednisolone and prednisone; AND
      ii. The patient has tried at least ONE systemic nonsteroidal anti-inflammatory agent (NSAID).
      Note: Examples of systemic NSAIDs include ibuprofen and naproxen; AND
      iii. The agent is prescribed by or in consultation with a rheumatologist or an oncologist.
   B) Patients Currently Receiving Actemra (IV or SC). Approve for 1 year if the patient has had a response, as determined by the prescriber.
      Note: Examples of response include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Actemra IV or SC.

7. **Still's Disease.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, and iii):
      i. The patient has tried one corticosteroid; AND
      ii. The patient has tried one conventional synthetic disease-modifying antirheumatic drug (DMARD) such as methotrexate (MTX) given for at least 2 months or was intolerant to a conventional synthetic DMARD; AND
      iii. The agent is prescribed by or in consultation with a rheumatologist.
   B) Patients Currently Receiving Actemra (IV or SC). Approve for 1 year if the patient has responded, as determined by the prescriber.
      Note: Examples of response include normalization of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or ferritin serum levels; decrease in number of tender or swollen joints; resolution of fever.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Actemra IV has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Data are lacking evaluating concomitant use of Actemra IV another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see **Appendix** for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMARDs has a potential for a higher rate of adverse effects and lack of controlled trial data in support of additive efficacy.[21-22]
   Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate [MTX], leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Actemra IV.

2. **Crohn's Disease.** In a 12-week pilot study conducted in Japan, 36 adults with active Crohn's disease (Crohn's Disease Activity Index [CDAI] ≥ 150 and increased CRP) were randomized, in a double-blind fashion to Actemra 8 mg/kg IV every 2 weeks; or alternating infusions of Actemra 8 mg/kg IV every 4 weeks and placebo (i.e., alternating with placebo every 2 weeks), or to placebo every 2 weeks.[23] At baseline the CDAI means ranged from 287 to 306. Patients had been treated with corticosteroids, mesalamine-type drugs, metronidazole, or elemental diet. Six patients in the placebo group, four patients on Actemra IV every 4 weeks and one patient on Actemra IV every 2 weeks dropped out. The mean reduction in the CDAI score in the Actemra 8 mg/kg IV every 2 week group was 88 points (from mean 306 to 218). Further studies are needed.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual revision	Add approval criteria for Inflammatory Arthritis associated with checkpoint inhibitors (3 months initial) if the patient has tried at least one steroid and at least one nonsteroidal anti-inflammatory drug and if prescribed by or in consultation with a rheumatologist or an oncologist; approval is for 1 year if patient is currently responding to therapy. Throughout the policy, references to Humira, Enbrel, and Rituxan were reworded as adalimumab, etanercept, and rituxumab products, respectively, with the innovator names listed as examples of these products. Renflexis and Erelzi were also added as respective examples of infliximab and etanercept products. Abatacept SC was added as an example of a biologic that a patient may have previously tried for Polyarticular Juvenile Idiopathic Arthritis. Kevzara was added as examples of a biologic that a patient may have previously tried for Rheumatoid Arthritis. For Systemic Juvenile Idiopathic Arthritis, the criterion that directs patients to a systemic agent prior to approval was reworded to clarify its intent such that patients are now directed to a systemic agent, with conventional synthetic disease-modifying antirheumatic drugs, corticosteroids, and nonsteroidal anti-inflammatory drugs listed as examples. A note was added that prior use of a biologic agent would count towards this requirement; previously, criteria were worded more generally as a "systemic" agent and both conventional and biologic agents were listed together as examples.	03/21/2018
Annual revision	**Rheumatoid Arthritis:** Add Truxima as an example of a rituximab product. **Inflammatory Arthritis Associated with Checkpoint Inhibitor Therapy:** Add Yervoy, Tecentriq, Bavencio, Imfinzi, and Libtayo as examples of checkpoint inhibitors. **Patient is Currently Taking (for Rheumatoid Arthritis, Systemic Juvenile Idiopathic Arthritis, Polyarticular Juvenile Idiopathic Arthritis:** To align with the medical policy, change duration of approval to 1 year (previously was 3 years). **Castleman's Disease:** To align with the medical policy, change initial approval to a 4 month duration. For continuation of therapy, require a response (criteria previously approved continuation of therapy if the patient was on therapy for ≥ 90 days). **Still's Disease:** To align with the medical policy, change initial approval to a 3 month duration. For continuation of therapy, require a response (criteria previously approved continuation of therapy if the patient was on therapy for ≥ 90 days).	03/27/2019
Annual revision	**Cytokine Release Syndrome:** This condition was clarified to specify that it must be Associated with Chimeric Antigen Receptor (CAR) T-Cell Therapy to qualify for this condition for coverage. A note was added to clarify that cases of CRS due to COVID-19 are to be referred to a separate condition for coverage (Other Uses With Supportive Evidence). Examples of chimeric antigen receptor T-cell therapy were moved to a Note in the policy (previously listed as examples within the criteria). **Polyarticular Juvenile Idiopathic Arthritis:** For the exception applying to patients with aggressive disease, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). Examples of one other agent tried for Polyarticular Juvenile Idiopathic Arthritis were moved to a Note in the policy (previously listed as examples within the criteria). Examples of biologics for Polyarticular Juvenile Idiopathic Arthritis were moved to be included in the Appendix (previously listed in a Note in the criteria section). Examples of an absolute contraindication to methotrexate, sulfasalazine, or leflunomide were move to a Note in the policy (previously listed as examples within the criteria). Examples of a response to therapy were moved to a Note in the policy (previously listed as examples within the criteria). **Rheumatoid Arthritis:** Examples of conventional synthetic disease-modifying antirheumatic drugs were moved to a Note in the policy (previously listed as examples within the criteria). Examples of biologics for Rheumatoid Arthritis were moved to be included in	03/25/2020

	the Appendix (previously listed in a Note in the criteria section). Examples of a response to therapy were moved to a Note in the policy (previously listed as examples within the criteria). **Systemic Juvenile Idiopathic Arthritis:** Examples of one other systemic agent tried for Systemic Juvenile Idiopathic Arthritis were moved to a Note in the policy (previously listed as examples within the criteria). Examples of a response to therapy were moved to a Note in the policy (previously listed as examples within the criteria). **Castleman's Disease:** For the exception applying to patients currently receiving Actemra who have responded, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). Examples of a response to therapy were moved to a Note in the policy (previously listed as examples within the criteria). **Inflammatory Arthritis Associated with Checkpoint Inhibitor Therapy:** Examples of a steroid were moved to a Note in the policy (previously listed as examples within the criteria). Examples of a nonsteroidal anti-inflammatory agent were moved to a Note in the policy (previously listed as examples within the criteria). Examples of a response to therapy were moved to a Note in the policy (previously listed as examples within the criteria). Criteria requiring a previous therapy were clarified to specify systemic therapies must have been tried (i.e., systemic corticosteroid, systemic NSAID). **Still's Disease:** For the exception applying to patients currently receiving Actemra who have responded, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). Examples of a response to therapy were moved to a Note in the policy (previously listed as examples within the criteria). **COVID-19:** This off-label indication was added to the policy as 1-week approval if the patient has cytokine release syndrome.	

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, PJIA, PsO, PsA, RA, SJIA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: PJIA, PSA, RA
		IV formulation: PJIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Ilaris (canakinumab SC injection**)**	Inhibition of IL-1β	SJIA
Kineret® (anakinra SC injection)	Inhibition of IL-1	RA, SJIA^
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA

Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; PJIA – Polyarticular juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; SJIA – Sytemice juvenile idiopathic arthritis; UC – Ulcerative colitis. ^ Off-label use of SJIA supported in guidelines.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Actemra® (tocilizumab for subcutaneous administration – Genentech/Roche)

DATE REVIEWED: 03/25/2020

OVERVIEW

Actemra for subcutaneous (SC) injection is a recombinant humanized interleukin-6 (IL-6) receptor inhibitor indicated for the following conditions:[1]

1. Rheumatoid arthritis (RA), for treatment of adults with moderate to severe active disease who have had an inadequate response to one or more disease modifying antirheumatic drugs (DMARDs); AND
2. Giant cell arteritis (GCA) in adults; AND
3. Polyarticular juvenile idiopathic arthritis (PJIA), for the treatment of active in patients 2 years of age and older; AND
4. Systemic juvenile idiopathic arthritis (SJIA), for the treatment of active disease in patients two years of age and older.

In RA and PJIA, Actemra SC can be given alone or in combination with methotrexate (MTX) [or with other nonbiologic DMARDs in RA]. Actemra is also available as an intravenous (IV) formulation which, in addition to RA and PJIA and SJIA, is indicated in chimeric antigen receptor (CAR) T-cell-induced severe or life-threatening cytokine release syndrome; however, the IV formulation is not indicated in GCA.

Disease Overview

IL-6 is a pro-inflammatory cytokine that is involved in various physiologic processes.[1] It has been shown to be involved in diverse physiological processes and is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as RA. Actemra binds to soluble and membrane-bound IL-6 receptors and has been shown to inhibit IL-6-mediated signaling through these receptors.

Clinical Efficacy

GCA and Polymyalgia Rheumatica (PMR)

In the pivotal trial evaluating Actemra SC for GCA (n = 251), patients were treated with corticosteroids in an open-label fashion (20 mg to 60 mg/day) during the screening period prior to treatment with Actemra SC.[2-3] Sustained remission at Week 52 was achieved in 56% of patients who received Actemra SC every week + 26-week prednisone taper and 53% of patients who received Actemra every other week + 26-week prednisone taper vs. in 14% of patients in the 26-week prednisone taper and 18% of patients in the 52-week prednisone taper. The pivotal trial evaluating Actemra SC for GCA allowed patients with the presence of

PMR and evidence of large-vessel vasculitis by angiography or imaging (e.g., magnetic resonance imaging [MRI], computed tomography angiography [CTA], positron emission tomography – computed tomography [PET/CT]) to be included in the study. This aligns with recent recommendations from the European League Against Rheumatism (EULAR) [2018] which state the diagnosis of GCA may be made without biopsy if there is a high suspicion of GCA and a positive imaging test.[4] Additional small studies and/or case reports support use of Actemra in patients with PMR without documented symptoms of GCA.[5-7]

Guidelines

Il-6 blockers are mentioned in multiple guidelines for treatment of inflammatory conditions.

- PJIA: The American College of Rheumatology (ACR)/Arthritis Foundation guidelines for the treatment of JIA (2019) specific to juvenile non-systemic polyarthritis, sacroiliitis, and enthesitis.[8] For patients without risk factors, initial therapy with a DMARD is conditionally recommended over a biologic (including Actemra). Biologics (e.g., Actemra) are conditionally recommended as initial treatment when combined with a DMARD over biologic monotherapy.
- SJIA: The 2013 update of the 2011 ACR recommendations for the treatment of SJIA mention Actemra as a second- or third-line agent in patients with active systemic features and varying degrees of synovitis and in patients without active systemic features and varying degrees of synovitis.[9] Nonsteroidal anti-inflammatory drugs NSAIDs, systemic glucocorticoids, Kineret, TNF inhibitors, and MTX are among other treatment options.
- RA: Guidelines from the ACR (2015) for the treatment of rheumatoid arthritis have tumor necrosis factor (TNF) inhibitors and non-TNF biologics (such as Actemra) equally positioned as a recommended therapy following a trial of a conventional synthetic DMARD (e.g., MTX, leflunomide, hydroxychloroquine, sulfasalazine).[10]

Safety

Actemra SC has Boxed Warnings regarding increased risk of developing serious infections which may lead to hospitalization or death. Patients who develop a serious infection should interrupt treatment with Actemra SC until infection is controlled. Patients should be monitored during and after treatment with Actemra SC, including tuberculosis.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Actemra SC. Because of the specialized skills required for evaluation and diagnosis of patients treated with Actemra SC as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Actemra SC to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the approval duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

All reviews for use of Actemra SC for COVID-19 and/or cytokine release syndrome associated with COVID-19 will be forwarded to the Medical Director.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Actemra SC is recommended in those who meet one of the following criteria:

FDA-Approved Indications

8. Giant Cell Arteritis (GCA). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following criteria (i and ii):

i. The patient has tried one systemic corticosteroid; AND
Note: An example of a systemic corticosteroid is prednisone.

ii. Actemra SC is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Actemra (IV or SC). Approve for 1 year if the patient has had a response, as determined by the prescriber.
Note: Examples of response include reduced corticosteroid dose, normalization of acute phase reactants (e.g., erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]), reduction or resolution of signs or symptoms of GCA. The patient may not have a full response, but there should have been a recent or past response to Actemra (SC or IV).

9. Polyarticular Juvenile Idiopathic Arthritis (PJIA). Approve for the duration noted if the patient meets ONE of the following (A or B):

B) Initial Therapy. Approve for 4 months if the patient meets BOTH of the following criteria (i and ii):

i. The patient meets one of the following conditions (a, b, c, or d):

e) The patient has tried one other agent for this condition.
Note: Examples of one other agent tried include methotrexate (MTX), sulfasalazine, leflunomide, or a nonsteroidal anti-inflammatory drug (NSAID). A biologic (refer to **Appendix** for examples of biologics used for JIA) also counts as a trial of one agent for JIA; OR

f) The patient will be starting on Actemra SC concurrently with methotrexate (MTX), sulfasalazine, or leflunomide; OR

g) The patient has an absolute contraindication to methotrexate (MTX), sulfasalazine, or leflunomide.
Note: Examples of absolute contraindication to methotrexate include pregnancy, breast feeding, alcoholic liver disease, immunodeficiency syndrome, and blood dyscrasias; OR

h) The patient has aggressive disease, as determined by the prescriber; AND

ii. Actemra SC is prescribed by or in consultation with a rheumatologist.

C) Patients Currently Receiving Actemra (IV or SC). Approve for 3 years if the patient has had a response, as determined by the prescriber.
Note: Examples of response include improvement in limitation of motion; less joint pain or tenderness; improved function or activities of daily living; decreased duration of morning stiffness or fatigue; reduced dosage of corticosteroids; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values. The patient may not have a full response, but there should have been a recent or past response to Actemra IV or SC.

10. Rheumatoid Arthritis (RA). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following criteria (i and ii):

i. The patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND
Note: Examples of one conventional DMARD tried include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already has a 3-month trial at least one biologic (refer to **Appendix** for examples of biologics used for RA). These patients who have already tried a biologic for RA are not required to "step back" and try a conventional synthetic DMARD.

ii. Actemra SC is prescribed by or in consultation with a rheumatologist.

B) Patients Currently Receiving Actemra (SC or IV). Approve for 3 years if the patient has had a response, as determined by the prescriber.
Note: Examples of response include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Actemra (SC or IV).

11. Systemic Juvenile Idiopathic Arthritis (SJIA). Approve for the duration noted if the patient meets ONE of the following (A or B):

C) Initial Therapy. Approve for 3 months if the patient meets the following criteria (i and ii):
- **i.** The patient has tried one other systemic agent for this condition; AND
  Note: Examples of one other systemic agent tried include a corticosteroid (oral, IV), a conventional synthetic disease-modifying antirheumatic drug (DMARD) [e.g., methotrexate {MTX}, leflunomide, sulfasalazine], or a 1-month trial of a nonsteroidal anti-inflammatory drug (NSAID). A previous trial of a biologic such as Kineret (anakinra SC injection), a tumor necrosis factor (TNF) inhibitor (e.g., an etanercept product, an adalimumab product, or an infliximb product, or Ilaris [canakinumab for SC injection]) also counts towards a trial of one other systemic agent for SJIA.
- **ii.** Actemra SC is prescribed by or in consultation with a rheumatologist.

D) Patients Currently Receiving Actemra (IV or SC). Approve for 3 years if the patient has had a response, as determined by the prescriber.
Note: Examples of response include improvement in limitation of motion; less joint pain or tenderness; decreased duration of morning stiffness or fatigue; improved function or activities of daily living; reduced dosage of corticosteroids; less joint pain or tenderness; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values. The patient may not have a full response, but there should have been a recent or past response to Actemra IV or SC.

Other Uses with Supportive Evidence

12. Polymyalgia Rheumatica (PMR). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets the following criteria (i and ii):
- **i.** The patient has tried one systemic corticosteroid.
  Note: An example of a systemic corticosteroid is prednisone; AND
- **ii.** Actemra SC is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Actemra (IV or SC). Approve for 1 year if the patient has had a response, as determined by the prescriber.
Note: Examples of response include reduced corticosteroid dose, normalization of acute phase reactants (e.g., erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]), reduction or resolution of signs or symptoms of PMR. The patient may not have a full response, but there should have been a recent or past response to Actemra (SC or IV).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Actemra SC has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Concurrent use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Data are lacking evaluating concomitant use of Actemra SC another biologics or with a targeted synthetic DMARD for an inflammatory condition (see **Appendix** for examples).[1,11] Combination therapy with biologics and/or biologics + targeted synthetic DMARDs has a potential for a higher rate of adverse effects and lack of controlled trial data in support of additive efficacy.[12] Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate (MTX), leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Actemra SC.

2. **COVID-19 (Coronavirus Disease 2019).** Forward all requests to the Medical Director.
   Note: This includes requests for cytokine release syndrome associated with COVID-19.

2. **Crohn's Disease.** In a 12-week pilot study conducted in Japan, 36 adults with active Crohn's disease (Crohn's Disease Activity Index [CDAI] ≥ 150 and increased C-reactive protein [CRP]) were randomized, in a double-blind fashion to IV Actemra 8 mg/kg every 2 weeks; or alternating infusions of Actemra 8 mg/kg every 4 weeks and placebo (i.e., alternating with placebo every 2 weeks), or to placebo every 2 weeks.[13] At baseline the CDAI means ranged from 287 to 306. Patients had been treated with corticosteroids, mesalamine-type drugs, metronidazole, or elemental diet. Six patients in the placebo group, 4 on Actemra every 4 weeks and 1 on Actemra every 2 weeks dropped out. The mean reduction in the CDAI score in the Actemra 8 mg/kg every 2 week group was 88 points – from mean 306 to 218. Further studies are needed.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Early annual revision	Add criteria for **Polyarticular Juvenile Idiopathic Arthritis**. Criteria approve for initial therapy (4 months) if prescribed by or in consultation with a rheumatologist, and if another therapy has been tried (e.g., methotrexate, sulfasalazine, or leflunomide, an nonsteroidal anti-inflammatory drug, or a biologic disease-modifying antirheumatic drug [prior use of a biologic agent would count towards this requirement]), or Actemra SC is started in combination with a conventional synthetic disease-modifying antirheumatic drug, or the patient has aggressive disease, as determined by the prescriber. Patients currently taking Actemra IV or SC can get authorization for 3 years if there has been a response to therapy. Due to the approval in Polyarticular Juvenile Idiopathic Arthritis, remove this indication from the conditions not recommended for coverage.	05/23/2018
Selected revision	**Polymyalgia Rheumatica:** Due to overlap of Giant Cell Arteritis and Polymyalgia Rheumatica and updated guidelines for diagnosis, remove requirement that patients with Polymyalgia Rheumaticahave imaging results suggestive of large vessel vasculitis.	09/05/2018
Selected revision	**Systemic Juvenile Idiopathic Arthritis:** Criteria were added to approve for this FDA-approved indication. Initial approval is for 3 months if a systemic agent has been tried, and if Actemra SC is prescribed by or in consultation with a rheumatologist. For patients currently taking Actemra IV or SC, the approval is for 3 years if the patient has responded to therapy. Due to this approval, Systemic Juvenile Idiopathic Arthritis was removed from the conditions not recommended for coverage.	09/19/2018
Early annual revision	**Rheumatoid Arthritis:** Add Truxima as an example of a rituximab product.	03/27/2019
Annual revision	**Giant Cell Arteritis:** Examples of one systemic corticosteroid were moved to a Note in the policy (previously listed as examples within the criteria). Examples of a response to therapy were moved to a Note in the policy (previously listed as examples within the criteria). **Polyarticular Juvenile Idiopathic Arthritis:** For the exception applying to patients with aggressive disease, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). Examples of one other agent tried for Polyarticular Juvenile Idiopathic Arthritis were moved to a Note in the policy (previously listed as examples within the criteria). Examples of biologics for Polyarticular Juvenile Idiopathic Arthritis were moved to be included in the Appendix (previously listed in a Note in the criteria section). Examples of an absolute contraindication to methotrexate, sulfasalazine, or leflunomide were move to a Note in the policy (previously listed as examples within the criteria). Examples of a response to therapy were moved to a Note in the policy (previously listed as examples within the criteria). **Rheumatoid Arthritis:** Examples of conventional synthetic disease-modifying antirheumatic drugs were moved to a Note in the policy (previously listed as examples within the criteria). Examples of biologics for rheumatoid arthritis were moved to be included in the Appendix (previously listed in a Note in the criteria section). Examples of a response to therapy were moved to a Note in the policy (previously listed as examples within the criteria). **Systemic Juvenile Idiopathic Arthritis:** Examples of one other systemic agent tried for Systemic Juvenile Idiopathic Arthritis were moved to a Note in the policy (previously listed as examples within the criteria). Examples of a response to therapy were moved to a Note in the policy (previously listed as examples within the criteria). **Polymyalgia Rheumatica:** Examples of systemic corticosteroids were moved to a Note in the policy (previously listed as examples within the criteria). Examples of a response to therapy were moved to a Note in the policy (previously listed as examples within the criteria).	03/25/2020

	COVID-19: This indication (including use in cytokine release syndrome associated with COVID-19) was added to the policy as a Condition Not Recommended for Coverage. All reviews are directed to the Medical Director.	

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, PJIA, PsO, PsA, RA, SJIA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: PJIA, PSA, RA
		IV formulation: PJIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Ilaris (canakinumab SC injection**)**	Inhibition of IL-1β	SJIA
Kineret® (anakinra SC injection)	Inhibition of IL-1	RA, SJIA^
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; PJIA – Polyarticular juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; SJIA – Sytemice juvenile idiopathic arthritis; UC – Ulcerative colitis. ^ Off-label use of SJIA supported in guidelines.

PRIOR AUTHORIZATION POLICY

POLICY: Gonadotropin-Releasing Hormone Agonists – Injectable Long-Acting Products Prior Authorization Policy

- Lupaneta Pack® (leuprolide acetate for depot suspension; norethindrone acetate tablets co-packaged for intramuscular use and oral use, respectively – AbbVie)
- Lupron Depot® (leuprolide acetate suspension for intramuscular injection – Abbott Laboratories)

REVIEW DATE: 01/20/2021; Selected revision 03/03/2021

Overview

Lupaneta Pack is indicated for initial management of the painful symptoms of **endometriosis** and for management of recurrence of symptoms.[1,2]

Lupron Depot (3.75 mg intramuscular (IM) injection every month, 11.25 mg IM injection every 3 months) is indicated for the following conditions:[3,4]

- Preoperative hematologic improvement of women with **anemia caused by uterine leiomyomata** (fibroids) for whom 3 months of hormonal suppression is deemed necessary. (Lupron Depot in combination with iron therapy).
- **Endometriosis**, including pain relief and reduction of endometriotic lesions (Lupron Depot monotherapy).
- **Endometriosis**, initial management of the painful symptoms of endometriosis and management of recurrence of symptoms (Lupron Depot in combination with norethindrone acetate 5 mg daily).

Lupron Depot (7.5 mg IM injection every month, 22.5 mg IM injection every 3 months, 30 mg IM injection every 4 months, and 45 mg IM injection every 6 months) is indicated for the **palliative treatment of advanced prostate cancer**.[5]

Duration of Treatment:

- Lupaneta Pack: Initial treatment course is limited to 6 months; a single retreatment course of up to 6 months is allowed. Total duration of treatment is limited to 12 months.[1,2]
- Lupron Depot 3.75 mg and 11.25 mg:[3,4]
  - Endometriosis: For the first 6 months of treatment, Lupron Depot may be used as monotherapy or in combination with norethindrone acetate. If retreatment is needed, Lupron Depot must be used in combination with norethindrone acetate (for 6 months). Total duration of treatment is limited to 12 months.
  - Uterine leiomyomata (fibroids): Recommended duration of treatment is up to 3 months.
- Lupron Depot 7.5 mg, 22.5 mg, 30 mg, and 45 mg: Labeling does not specify a treatment duration.

Guidelines

Abnormal Uterine Bleeding/Uterine Leiomyomata (Fibroids)

The American College of Obstetricians and Gynecologists (ACOG) practice bulletin regarding the diagnosis of abnormal uterine bleeding in reproductive-aged women discusses the nomenclature of abnormal uterine bleeding. It can be classified by the acronym PALM-COEIN (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified) and can be further classified by etiology.[6] The term abnormal uterine bleeding can also be paired with descriptive terms that describe the associated bleeding pattern such as heavy menstrual bleeding or intermenstrual bleeding.

The ACOG frequently asked questions (FAQ) #074 (2018) addresses medication use for the treatment of fibroids.[7] Gonadotropin-releasing hormone (GnRH) agonists are noted as medications that can stop the menstrual cycle and shrink fibroids. GnRH analogs are used as short-term preoperative therapy to reduce uterine and leiomyoma volume; long-term therapy should be limited to patients who have contraindications to other medical or surgical treatments.[8] They can also be used for acute abnormal uterine bleeding with an aromatase inhibitor or antagonist to prevent initial estrogen flare and for the treatment of heavy menstrual bleeding caused by leiomyoma-associated hormonal imbalance.[9]

A clinical practice guideline from the Society of Obstetricians and Gynaecologists of Canada notes that leuprolide acetate or combined hormonal contraception should be considered highly effective in preventing abnormal uterine bleeding when initiated prior to cancer treatment in premenopausal women at risk of

thrombocytopenia.[10] The ACOG committee opinion on prevention and management of heavy menstrual bleeding in adolescent patients undergoing cancer treatment lists leuprolide as an option for patients.[11]

Endometriosis

According to the ACOG practice bulletin on the management of endometriosis (2010, reaffirmed 2018), empiric therapy with a 3-month course of a gonadotropin-releasing hormone (GnRH) agonist is appropriate after an appropriate pretreatment evaluation (to exclude other causes of chronic pelvic pain) and failure of initial treatment with oral contraceptives and nonsteroidal anti-inflammatory drugs (NSAIDs).[12]

Other Uses With Supportive Evidence

The Endocrine Society Guideline (2017) for the Treatment of Gender-Dysphoric/Gender-Incongruent Persons note that persons who fulfill criteria for treatment and who request treatment should initially undergo treatment to suppress physical changes of puberty.[13] Pubertal hormonal suppression should typically be initiated after the adolescent first exhibits physical changes of puberty (Tanner stages G2/B2). However, there may be compelling reasons to initiate hormone treatment before the age of 16 years in some adolescents. The guidelines note suppression of pubertal development and gonadal function can be effectively achieved via gonadotropin suppression using GnRH analogs. Long-acting GnRH analogs are the currently preferred treatment option. An advantage to using a GnRH analog is that the effects can be reversed; pubertal suppression can be discontinued if the individual no longer wishes to transition. Upon discontinuation of therapy, spontaneous pubertal development has been shown to resume. The World Professional Association for Transgender Health (WPATH) Standards of Care (version 7) document also recommends the use of GnRH analogs in both male and female adolescents as a fully reversible intervention for pubertal suppression.[14] GnRH can also be used in patients during late puberty to suppress the hypothalamic-pituitary-gonadal axis to allow for lower doses of cross-sex hormones.[15] In addition to use in adolescents, GnRH analog therapy is also used in adults, particularly male-to-female patients.[16]

In addition to the approved indications, GnRH agonists such as long-acting leuprolide, have been used for other conditions. The National Comprehensive Cancer Network (NCCN) guidelines for Adolescent and Young Adult Oncology (version 1.2021 – September 10, 2020) note there are some data to suggest menstrual suppression with GnRH agonists (before the initiation of chemotherapy) may protect ovaries in young women with breast cancer.[17] There are conflicting data regarding the beneficial effects of GnRH agonists on fertility preservation. The NCCN guidelines for Breast Cancer (version 6.2020 – September 8, 2020) note that luteinizing hormone-releasing hormone agonists, such as leuprolide, can be used for ovarian suppression.[18] The guidelines further note that randomized trials have shown that ovarian suppression with GnRH agonist therapy administered during adjuvant chemotherapy in premenopausal women with breast tumors (regardless of hormone receptor status) may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhea. The NCCN guidelines for Head and Neck Cancer (version 1.2021 – November 9, 2020) recommend the use of androgen receptor therapy (i.e., leuprolide, bicalutamide) for androgen receptor-positive, advanced salivary gland tumors with distant metastases.[19] The NCCN guidelines for Ovarian Cancer including Fallopian Tube Cancer and Primary Peritoneal Cancer (version 2.2020 – January 12, 2021) recommend leuprolide as a hormonal therapy option in various settings (e.g., adjuvant therapy, recurrence).[20]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lupaneta Pack and Lupron-Depot. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lupaneta Pack and Lupron-Depot as well as the monitoring required for adverse events and long-term efficacy, approval for some of the conditions requires Lupaneta Pack and Lupron-Depot to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

Recommended Authorization Criteria

Coverage of Lupaneta Pack and Lupron Depot is recommended in those who meet the following criteria:

FDA-Approved Indications

36. Endometriosis. Approve Lupron Depot or Lupaneta Pack for 1 year if the patient has tried one of the following (A, B, or C):
- **D)** A contraceptive (e.g., combination oral contraceptives, levonorgestrel-releasing intrauterine systems [e.g., Mirena®, Liletta®]), OR
- **E)** An oral progesterone (e.g., norethindrone tablets), OR
- **F)** A depo-medroxyprogesterone injection, unless contraindicated.

NOTE: An exception to the requirement for a trial of the above therapies can be made if the patient has previously used a gonadotropin-releasing hormone [GnRH] agonist (e.g., Lupron-Depot) or antagonist (e.g., Orilissa).

37. Prostate Cancer. Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.

38. Uterine Leiomyomata (fibroids). Approve Lupron Depot for 3 months.

Other Uses with Supportive Evidence

39. Abnormal Uterine Bleeding. Approve Lupron Depot for 6 months.

40. Breast Cancer. Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.

41. Gender Dysphoric/Gender-Incongruent Persons; Persons Undergoing Gender Reassignment (Female-To-Male [FTM] or Male-To-Female [MTF]). Approve Lupron Depot for 1 year if prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of transgender patients.

42. Head and Neck Cancer – Salivary Gland Tumors. Approve Lupron Depot for 1 year if the patient meets the following criteria (A, B, and C):
- **D)** Patient has advanced salivary gland tumors with distant metastases; AND
- **E)** Patient has androgen receptor (AR)-positive disease; AND
- **F)** The medication is prescribed by or in consultation with an oncologist.

43. Ovarian Cancer. Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.

44. Preservation of Ovarian Function/Fertility in Patients Undergoing Chemotherapy. Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.

45. Prophylaxis or Treatment of Uterine Bleeding in Patients with Hematologic Malignancy, or Undergoing Cancer Treatment, or Prior to Bone Marrow/Stem Cell Transplantation (BMT/SCT). Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lupron Depot and Lupaneta Pack is not recommended in the following situations:

65. Hirsutism. The Endocrine Society guidelines (2018) on the treatment of hirsutism in premenopausal women suggest against using GnRH agonists except in women with severe forms of hyperandrogenemia, such as ovarian hyperthecosis, who have had a suboptimal response to oral contraceptives and antiandrogens.[21]

66. Menstrual Migraine. A review article notes that GnRH analogs are effective in eliminating menstrual migraines, but their use is limited due to the significant adverse effects of estrogen deficiency, including severe vasomotor symptoms, sleep disruption, and a marked reduction in bone density.[22,23]

67. Premenstrual Syndrome (PMS). On occasion, GnRH analogs are recommended as an aid in the diagnosis of PMS.[24] Use of GnRH analogs results in profound cycle suppression and elimination of PMS symptoms, but these agents should not be used routinely. GnRH analogs are recommended only as a third-line treatment or for the most refractory patients.

68. Polycystic Ovarian Syndrome (PCOS). PCOS guidelines from the Endocrine Society (2013)[25] and review articles[26,27] do not recommend this as a treatment modality.

69. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	• Removal of Lupron Depot-Ped and Triptodur and the indication of central precocious puberty. These medications are addressed in the policy: Gonadotropin-Releasing Hormone Agonists for Central Precocious Puberty PA Policy with Preferred Step Therapy. • Updated the following indication, Prophylaxis or Treatment of Uterine Bleeding in Patients with Hematologic Malignancy or Prior to Bone Marrow/Stem Cell Transplantation to include patients undergoing cancer treatment. • Added "if prescribed by or in consultation with an oncologist" to the following diagnoses: Prostate Cancer, Ovarian Cancer, Breast Cancer, Preserve Ovarian Function/Fertility in Patients undergoing Chemotherapy, and Prophylaxis or Treatment of Uterine Bleeding in Patients with Hematologic Malignancy or Undergoing Cancer Treatment, or Prior to Bone Marrow/Stem Cell Transplantation to align with the Lupron Depot Medical Benefit Management policy.	1/30/2019
Selected Revision	• Updated endometriosis criterion: removal of continued pain criteria and removal of prescriber's specialty or consultation specialty. • Added the wording Gender Dysphoric/Gender Incongruent Persons to the diagnosis for Gender Reassignment.	4/10/2019
Annual Revision	No criteria changes.	01/15/2020
Update	09/22/2020: Revised policy name from "Gonadotropin-Releasing Hormone Agonists – Injectable Long-Acting Products (Lupron Depot and Lupaneta Pack) Prior Authorization Policy" to "Gonadotropin-Releasing Hormone Agonists – Injectable Long-Acting Products Prior Authorization Policy".	--
Annual Revision	Head and Neck Cancer – Salivary Gland Tumors: revised "Patient has recurrent disease with distant metastases" to "Patient has advanced salivary gland tumors with distant metastases".	01/20/2021
Selected Revision	Lupron Depot 3.75 mg and 11.25 mg – Uterine leiomyomata (fibroids): Approval duration is changed from 6 months to 3 months, due to revised labeling.	03/03/2021

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Arcalyst Prior Authorization Policy

- Arcalyst® (rilonacept for subcutaneous injection – Regeneron Pharmaceuticals)

REVIEW DATE: 01/20/2021

OVERVIEW

Arcalyst, an interleukin-1 (IL-1) blocker, is indicated for the following uses:[1]

- **Cryopyrin-associated periodic syndromes (CAPS)**, including familial cold autoinflammatory syndrome and Muckle-Wells Syndrome, for treatment of patients ≥ 12 years of age.
- **Deficiency of interleukin-1 receptor antagonist (DIRA),** for maintenance of remission in patients weighing at least 10 kg.

In the pivotal trial for CAPS, patients had significant improvement in symptoms scores were improved with Arcalyst through Week 6 and were maintained through Week 15. In the pivotal trial for DIRA, enrolled patients with a loss of function *IL1RN* mutation who previously experienced a benefit with Kineret (anakinra subcutaneous injection). All patients (n = 6) were in remission at Month 6 and sustained remission for the remainder of the 2-year study.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Arcalyst. Because of the specialized skills required for evaluation and diagnosis of patients treated with Arcalyst as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Arcalyst to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

All reviews for use of Arcalyst for COVID-19 and/or cytokine release syndrome associated with COVID-19 will be forwarded to the Medical Director.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Arcalyst is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Cryopyrin-Associated Periodic Syndromes.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   Note: This includes Familial Cold Autoinflammatory Syndrome, Muckle-Wells Syndrome, and Neonatal Onset Multisystem Inflammatory Disease or chronic infantile neurological cutaneous and articular syndrome.
   - **A)** Initial Therapy. Approve for 3 months if the patient meets the following conditions (i and ii):
     - **i.** Patient is ≥ 12 years of age; AND
     - **ii.** The medication is prescribed by or in consultation with a rheumatologist, geneticist, allergist/immunologist, or dermatologist.
   - **B)** Patient is Currently Receiving Arcalyst. Approve for 3 years if the patient has had a response, as determined by the prescriber.

2. **Deficiency of Interleukin-1 Receptor Antagonist**. Approve for the duration noted if the patient meets one of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 10 kg (22 pounds); AND
     - **ii.** Genetic testing has confirmed a mutation in the *IL1RN* gene; AND
     - **iii.** According to the prescriber, patient has demonstrated a clinical benefit with Kineret (anakinra subcutaneous injection); AND
       Note: Examples of a clinical response with Kineret include normalized acute phase reactants; resolution of fever, skin rash, and bone pain; and reduced dosage of corticosteroids.
     - **iv.** The medication is prescribed by or in consultation with a rheumatologist, geneticist, dermatologist, or a physician specializing in the treatment of autoinflammatory disorders.
   - **B)** Patient is Currently Receiving Arcalyst. Approve for 3 years if the patient has responded to therapy, as determined by the prescriber.
     Note: Examples include sustained remission; continued resolution of fever, skin rash, and bone pain; normalized acute phase reactants.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Arcalyst is not recommended in the following situations:

70. **Concurrent Biologic Therapy.** Arcalyst should not be administered in combination with another biologic agent for an inflammatory condition (see Appendix for examples).[1] Arcalyst has not been used in combination with tumor necrosis factor inhibitors (TNFis). An increased incidence of serious infections has been associated with another interleukin-1 blocker (Kineret® [anakinra subcutaneous injection]) when given in combination with TNFis.

71. **COVID-19 (Coronavirus Disease 2019).** Forward all requests to the Medical Director.
Note: This includes requests for cytokine release syndrome associated with COVID-19.

72. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Arcalyst® for injection [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals Inc; December 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/06/2019
Selected Revision	**COVID-19:** This indication (including use in cytokine release syndrome associated with COVID-19) was added to the policy as a Condition Not Recommended for Coverage. All reviews are directed to the Medical Director.	04/01/2020
Annual Revision	No criteria changes.	11/18/2020
Early Annual Revision	**Deficiency of Interleukin-1 Receptor Antagonist:** Criteira for this newly approved condition were added to the policy. For an initial 6-month approval, the patient must weigh ≥ 22 kg, genetic testing must have confirmed a mutation in the *IL1RN* gene, and the patient must have tried Kineret. Additionally, Arcalyst must be prescribed by or in consultation with a specialist. For a patient currently taking Arcalyst, a 3-year approval is authorized in the patient has responded to therapy.	01/20/2021

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, PJIA, PsO, PsA, RA, SJIA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: PJIA, PSA, RA
		IV formulation: PJIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Ilaris (canakinumab SC injection**)**	Inhibition of IL-1β	SJIA
Kineret® (anakinra SC injection)	Inhibition of IL-1	RA, SJIA^
	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC

Stelara® (ustekinumab SC injection, ustekinumab IV infusion)		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; PJIA – Polyarticular juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; SJIA – Systemic juvenile idiopathic arthritis; UC – Ulcerative colitis; ^ Off-label use of SJIA supported in guidelines.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Cimzia Prior Authorization Policy

- Cimzia® (certolizumab pegol for subcutaneous injection [lyophilized powder or solution] – UCB)

REVIEW DATE: 02/24/2021

OVERVIEW

Cimzia, a tumor necrosis factor inhibitor (TNFi), is indicated for the following uses:[1]

- **Ankylosing spondylitis**, for the treatment of adults with active disease.
- **Crohn's disease**, for reducing signs and symptoms and maintaining clinical responses in adults with moderate to severe active disease who have had an inadequate response to conventional therapy.
- **Non-radiographic axial spondyloarthritis**, in patients with objective signs of inflammation.
- **Plaque psoriasis**, for the treatment of adults with moderately to severely active disease who are candidates for systemic therapy or phototherapy.
- **Psoriatic arthritis**, for the treatment of adult patients with active disease.
- **Rheumatoid arthritis**, for the treatment of adults with moderately to severely active disease.

Cimzia may be used as monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).

Dosing Information

Approved induction dosing is 400 mg given subcutaneously at Weeks 0, 2, and 4. For psoriasis, maintenance dosing is 400 mg given every 2 weeks. For other indications, maintenance dosing is generally given as 400 mg subcutaneously per 28-day period. This dose may be administered as a single 200-mg injection given once every 2 weeks or as two 200-mg doses (400-mg dose) given once every 4 weeks.

Guidelines

TNFis feature prominently in guidelines for treatment of inflammatory conditions.

- **Crohn's Disease:** The American College of Gastroenterology has guidelines for Crohn's disease (2018).[3] TNFis are listed as an option for disease that is resistant to corticosteroids, severely active disease, perianal fistulizing disease, and maintenance of remission. In post-operative Crohn's disease, a TNFi should be started within 4 weeks of surgery to prevent recurrence.
- **Plaque Psoriasis:** Guidelines from the American Academy of Dermatologists and National Psoriasis Foundation (2019) recommend TNFis as a monotherapy treatment option for adults with moderate to severe disease.[4] Based on extrapolation of data, Cimzia is likely to have class characteristics similar to the other TNFis.
- **Psoriatic Arthritis:** Guidelines from ACR (2019) recommend TNFis over other biologics for use in treatment-naïve patients with PsA and in those who were previously treated with an oral therapy.[5]
- **Rheumatoid Arthritis:** Guidelines from the American College of Rheumatology (ACR) [2015] have TNF inhibitors and non-TNF biologics, administered with or without MTX, equally positioned as a recommended therapy following a trial of a conventional synthetic DMARD (e.g., MTX, leflunomide, hydroxychloroquine, sulfasalazine).[6]
- **Spondyloarthritis:** Guidelines for ankylosing spondylitis and nonradiographic axial spondyloarthritis are published by the American College of Rheumatology (ACR)/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (2019).[2] TNFis are recommended for the initial biologic. In those who are secondary nonresponders to a TNFi, a second TNFi is recommended over switching out of the class.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cimzia. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cimzia as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Cimzia to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cimzia is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Ankylosing Spondylitis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if prescribed by or in consultation with a rheumatologist.
   - **B)** Patient is Currently Receiving Cimzia. Approve for 3 years if the patient had a response, as determined by the prescriber.

     Note: Examples of a response include decreased pain or stiffness, improved function or activities of daily living. The patient may not have a full response, but there should have been a recent or past response to Cimzia.

2. **Crohn's Disease.** Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient meets one of the following (a or b):
  - **a)** Patient has tried or is currently taking corticosteroids, or corticosteroids are contraindicated in this patient; OR
  - **b)** Patient has tried one other conventional systemic therapy for Crohn's disease; AND
    Note: Examples of systemic therapies for Crohn's disease include azathioprine, 6-mercaptopurine, and methotrexate. A previous trial of a biologic also counts as a trial of one other agent for Crohn's disease. Refer to Appendix for examples of biologics used for Crohn's disease. A trial of mesalamine does not count as a systemic agent for Crohn's disease.

- **iii.** The medication is prescribed by or in consultation with a gastroenterologist.

B) Patient is Currently Receiving Cimzia. Approve for 3 years if the patient had a response, as determined by the prescriber.
Note: The patient may not have a full response, but there should have been a recent or past response to Cimzia. A patient with fistulizing Crohn's disease or Crohn's disease of the ileal pouch must meet the above criteria for Crohn's disease.

3. Non-Radiographic Axial Spondyloarthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (i and ii):
- **i.** Patient has objective signs of inflammation, defined as at least one of the following (a or b):
  - **a)** C-reactive protein (CRP) elevated beyond the upper limit of normal for the reporting laboratory; OR
  - **b)** Sacroiliitis reported on magnetic resonance imaging (MRI); AND
- **ii.** The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Cimzia. Approve for 3 years if the patient had a response, as determined by the prescriber.
Note: Examples of a response include decreased pain or stiffness, improved function or activities of daily living. The patient may not have a full response, but there should have been a recent or past response to Cimzia.

4. Plaque Psoriasis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient meets ONE of the following conditions (a or b):
  - **a)** Patient has tried at least at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR
    Note: Examples of traditional systemic agents for psoriasis include methotrexate, cyclosporine, acitretin tablets, or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already had a 3-month trial or previous intolerance to at least one biologic. Refer to Appendix for examples of biologics used for psoriasis. A patient who has already tried a biologic for psoriasis is not required to "step back" and try a traditional systemic agent for psoriasis.
  - **b)** Patient has a contraindication to methotrexate, as determined by the prescriber; AND
- **iii.** The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Cimzia. Approve for 3 years if the patient had a response, as determined by the prescriber.

Note: The patient may not have a full response, but there should have been a recent or past response to Cimzia.

5. **Psoriatic Arthritis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if prescribed by or in consultation with a rheumatologist or a dermatologist.
   - **B)** Patient is Currently Receiving Cimzia. Approve for 3 years if the patient had a response, as determined by the prescriber.

     Note: Examples of a response include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improvements in acute phase reactants (for example, C-reactive protein). The patient may not have a full response, but there should have been a recent or past response to Cimzia.

6. **Rheumatoid Arthritis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets the following (i and ii):
     - **i.** Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND

       Note: Examples of conventional synthetic DMARDs include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already had a 3-month trial at least one biologic. Refer to Appendix for examples of biologics used for rheumatoid arthritis. A patient who has already tried a biologic for rheumatoid arthritis is not required to "step back" and try a conventional synthetic DMARD.
     - **ii.** The medication is prescribed by or in consultation with a rheumatologist.
   - **B)** Patient is Currently Receiving Cimzia. Approve for 3 years if the patient had a response, as determined by the prescriber.

     Note: Examples of a response include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Cimzia.

Other Uses with Supportive Evidence

7. **Spondyloarthritis, Other Subtypes** Approve for the duration noted if the patient meets ONE of the following conditions (A or B):

   Note: Examples of other subtypes of spondyloarthritis include undifferentiated arthritis and reactive arthritis (Reiter's disease). For ankylosing spondylitis, psoriatic arthritis, or non-radiographic axial spondyloarthrits, refer to the respective criteria under FDA-approved indications.
   - **A)** Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient has arthritis primarily in the knees, ankles, elbows, wrists, hands, and/or feet; AND
     - **ii.** Patient has tried at least ONE conventional synthetic disease-modifying antirheumatic drug (DMARD); AND

       Note: Examples include methotrexate, leflunomide, and sulfasalazine.

iii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Cimzia. Approve for 1 year if the patient had a response, as determined by the prescriber.
Note: Examples of a response include decreased pain or stiffness, improved function or activities of daily living. The patient may not have a full response, but there should have been a recent or past response to Cimzia.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cimzia is not recommended in the following situations:

1. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Cimzia should not be administered in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see Appendix for examples). Combination therapy is generally not recommended due to a potentially higher rate of AEs with combinations and lack of data supportive of additional efficacy.[7,8] Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Cimzia.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Cimzia® for injection [prescribing information]. Smyrna, GA: UCB, Inc.; September 2019.
2. Ward MM, Deodhar A, Gensler LS, et al. 2019 update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Rheumatol*. 2019;71(10):1599-1613.
3. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: management of Crohn's Disease in adults. *Am J Gastroenterol*. 2018:113(4):481-517.
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7. Furst DE, Keystone EC, So AK, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2012. *Ann Rheum Dis*. 2013;72 Suppl 2:ii2-34.
8. Xeljanz® tablets [prescribing information]. New York, NY: Pfizer Inc; February 2016.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Non-Radiographic Axial Spondylitis (nr-axSpA):** Due to approval in this condition, criteria were moved from Other Conditions Recommended for Coverage to the FDA-Approved indications section of the policy. To align with the indication, criteria were added to require objective signs of inflammation, defined as C-reactive protein (CRP) elevated beyond the upper limit of normal for the reporting laboratory or sacroiliitis reported on magnetic resonance imaging. For patients continuing therapy, the approval duration was changed to 3 years (previously was 1 year), and applies to patients who are responding to therapy (previously criteria also required the patient to be on Cimzia for ≥ 90 days). **Spondyloarthritis (SpA), Other Subtypes:** Due to Cimzia's approval in nr-axSpA, this off-label approval condition was reworded (previously listed as Spondyloarthritis, Subtypes Other than Ankylosing Spondylitis or Psoriatic Arthritis). There is a note which directs to criteria for FDA-approved subtypes of SpA (AS, PsA, and nr-axSpA).	04/24/2019

	Criteria which approved for patients with primarily axial disease were removed. Criteria were changed to approve for 3 months for patients starting therapy (previously was 1 year). For patients currently receiving therapy, examples of a response to therapy were added; the requirement that patients be on Cimzia for ≥ 90 days was removed.	
Annual Revision	**Ankylosing Spondylitis:** For patients continuing therapy, examples of a response were moved to a note in the policy (previously listed in the criteria for patients continuing therapy). **Crohn's Disease:** The requirement that the patient is an adult was moved into the criteria section for initial therapy. Criteria were clarified to define adult as a patient ≥ 18 years of age. Previously, the requirement that the patient was an adult was listed as part of the diagnosis (i.e., previously listed as Crohn's disease in an adult) and applied to initial and continuation of therapy. Criteria were clarified to state that previously tried therapies for Crohn's disease must have been systemic therapies. Examples of systemic agents were moved to a Note (previously listed as examples within the criteria). Examples of biologics for Crohn's disease were moved to be included in the Appendix (previously listed in a Note in the criteria section). A clarification was also added that mesalamine does not count towards a trial of a systemic therapy. **Non-Radiographic Axial Spondyloarthritis:** Examples of a response to therapy were moved to a Note (previously listed as examples within the criteria). **Plaque Psoriasis:** Examples of traditional systemic agents were moved to a Note (previously listed as examples within the criteria). Examples of biologics for plaque psoriasis were moved to be included in the Appendix (previously listed in a Note in the criteria section). Examples of an absolute contraindication to methotrexate, sulfasalazine, or leflunomide were moved to a Note (previously listed as examples within the criteria). For the exception applying to patients with a contraindication to methotrexate, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). **Psoriatic Arthritis:** For patients continuing therapy, examples of a response were moved to a note in the policy (previously listed in the criteria for patients continuing therapy). **Rheumatoid Arthritis:** Examples of conventional synthetic disease-modifying antirheumatic drugs were moved to a Note (previously listed as examples within the criteria). Examples of biologics for Rheumatoid Arthritis were moved to be included in the Appendix (previously listed in a Note in the criteria section). Examples of a response to therapy were moved to a Note (previously listed as examples within the criteria). **Spondyloarthritis (SpA), Other Subtypes:** Examples of conventional synthetic disease-modifying antirheumatic drugs were moved to a Note (previously listed as examples within the criteria). Examples of a response to therapy were moved to a Note (previously listed as examples within the criteria).	04/22/2020
Early Annual Revision	**Crohn's Disease:** To align with other similarly worded policies, wording was changed to specify that previous therapy must have been a conventional systemic therapy (previously required a trial of a systemic agent, with conventional systemic therapies among the examples). **Spondyloarthritis, Other Subtypes:** Examples of other subtypes of spondyloarthritis were moved to a note (previously listed as examples within the indication).	02/24/2021

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA

Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of JAK pathways	RA
Xeljanz® (tofacitinib tablets)	Inhibition of JAK pathways	RA, PJIA, PsA, UC
Xeljanz® XR (tofacitinib extended-release tablets)	Inhibition of JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; ^ Off-label use of Kineret in JIA supported in guidelines; DMARDs – Disease-modifying antirheumatic drug.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Cosentyx Prior Authorization Policy
- Cosentyx® (secukinumab for subcutaneous injection – Novartis)

REVIEW DATE: 03/04/2020; selected revision 06/24/2020

OVERVIEW

Cosentyx, a human interleukin (IL)-17A antagonist, is indicated in the following conditions:[1]
- **Plaque psoriasis**, in adults with moderate to severe disease who are candidates for systemic therapy or phototherapy.
- **Psoriatic arthritis**, in adults with active disease (given ± methotrexate).
- **Ankylosing spondylitis**, in adults with active disease.
- **Non-radiographic axial spondyloarthritis**, in adults with active disease and objective signs of inflammation.

Safety and efficacy in patients ≤ 18 years of age has not been established. In the pivotal trial for non-radiographic axial spondyloarthritis, patients were required to have objective signs of inflammation, indicated by elevated C-reactive protein and/or sacroiliitis on magnetic resonance imaging.

Guidelines

Il-17 blockers are mentioned in multiple guidelines for treatment of inflammatory conditions. Guidelines recommend assessment of response to initial therapy, most often following 3 months of therapy.
- **Spondyloarthritis:** Guidelines for ankylosing spondylitis and non-radiographic axial spondyloarthritis are published by the American College of Rheumatology (ACR)/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (2019).[2] Following

primary nonresponse to a tumor necrosis factor inhibitor (TNFi), either Cosentyx or Taltz is recommended; however, if the patient is a secondary nonresponder, a second TNFi is recommended over switching out of the class. In patients with a contraindication to a TNFi, use of an IL-17 blocker is recommended over traditional oral agents such as methotrexate or sulfasalazine.

- **Plaque Psoriasis:** Joint guidelines of care for the management and treatment of psoriasis with biologics were published by the American Academy of Dermatology (AAD) and the National Psoriasis Foundation (2019).[3] All of the biologics are generally recommended for treatment of moderate to severe disease. The AAD also recommends methotrexate (unless contraindicated) and other systemic therapies for treatment of moderate to severe psoriasis.[4] Traditional systemic agents can benefit widespread psoriasis. Studies have assessed response to methotrexate following 6 weeks to 4 months of treatment.
- **Psoriatic Arthritis:** Guidelines from the ACR/National Psoriasis Foundation (2018) generally recommend TNFis as the first-line treatment strategy over other biologics (e.g., IL-17 blockers) with differing mechanisms of action.[5]

Safety

Warnings/Precautions for Cosentyx include infections, pre-treatment evaluation for tuberculosis, exacerbation of Crohn's disease, hypersensitivity reactions, risk of hypersensitivity in latex-sensitive individuals, and vaccinations.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cosentyx. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cosentyx as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Cosentyx to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cosentyx is recommended in those who meet the following criteria:

FDA-Approved Indications

D) Ankylosing Spondylitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

- **A)** Initial Therapy. Approve for 3 months if Cosentyx is prescribed by or in consultation with a rheumatologist.
- **B)** Patient is Currently Receiving Cosentyx. Approve for 3 years if the patient has had a response, as determined by the prescriber.
  Note: Examples of a response include decreased pain or stiffness, improved function or activities of daily living. The patient may not have a full response, but there should have been a recent or past response to Cosentyx.

E) Non-Radiographic Axial Spondyloarthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

- **A)** Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (i and ii):
  - **i.** Patient has objective signs of inflammation, defined as at least one of the following (a or b):
    - **a)** C-reactive protein elevated beyond the upper limit of normal for the reporting laboratory; OR
    - **b)** Sacroiliitis reported on magnetic resonance imaging; AND
  - **ii.** Cosentyx is prescribed by or in consultation with a rheumatologist.
- **B)** Patient is Currently Receiving Cosentyx. Approve for 3 years if the patient has had a response, as determined by the prescriber.
  Note: Examples of a response include decreased pain or stiffness, improved function or activities of daily living. The patient may not have a full response, but there should have been a recent or past response to Cosentyx.

F) Plaque Psoriasis. Approve for the duration noted if the patient meets ONE of the following (A or B):

- **A)** Initial Therapy. Approve for 3 months if the patient meets ALL of the following criteria (i, ii, and iii):
  - **i.** Patient is ≥ 18 years of age; AND
  - **ii.** Patient meets ONE of the following conditions (a or b):
    - **1.** Patient has tried at least at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR
      Note: Examples include methotrexate, cyclosporine, acitretin, or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already has a 3-month trial or previous intolerance to at least one biologic for this condition. (Refer to **Appendix** for examples of

biologics used for psoriasis.) These patients who have already tried a biologic for psoriasis are not required to "step back" and try a traditional systemic agent for psoriasis).

2. Patient has a contraindication to methotrexate, as determined by the prescriber; AND

iii. Cosentyx is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Cosentyx. Approve for 3 years if the patient has responded, as determined by the prescriber.
Note: Patient may not have a full response, but there should have been a recent or past response to Cosentyx.

G) Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if Cosentyx is prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving Cosentyx. Approve for 3 years if the patient has responded, as determined by the prescriber.
Note: Examples of a response include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improvements in acute phase reactants (for example, C-reactive protein). The patient may not have a full response, but there should have been a recent or past response to Cosentyx.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cosentyx is not recommended in the following situations:

1. **Concurrent Use with other Biologics or Targeted Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs).** Cosentyx should not be administered in combination with another biologic or targeted synthetic DMARD used for an inflammatory condition (See Appendix for examples). Combination therapy is generally not recommended due to a potential for a higher rate of adverse effects with combinations and lack of evidence for additive efficacy.
Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Cosentyx.

73. **Crohn's Disease.** Exacerbations of Crohn's disease, in some cases serious, occurred in clinical trials with Cosentyx-treated patients.[1] In a Phase II published study in patients with Crohn's disease (n = 59), an intravenous formulation of Cosentyx did not reduce the Crohn's disease activity index by ≥ 50 points compared with placebo and the study was terminated prematurely.[6]

74. Patients < 18 Years of Age. Cosentyx is indicated in adults ≥ 18 years of age. Safety and efficacy in pediatric patients have not been established.[1]

75. Rheumatoid Arthritis. In a published, double-dummy Phase III study, Cosentyx was less effective that current treatments in patients with rheumatoid arthritis who were previously treated with a TNFi.[7] Patients were randomized to one of four treatment groups: 1) induction with an intravenous formulation of Cosentyx (10 mg/kg) followed by Cosentyx 150 mg subcutaneously given once every 4 weeks Q4W) [n = 137]; 2) secukinumab intravenous induction (10 mg/kg) followed by Cosentyx 75 mg subcutaneously Q4W (n = 138). At Week 24, ACR 20 response was significantly better with Cosentyx 150 mg subcutaneously (31%) and Orencia intravenous (43%) vs. placebo (18%). ACR 20 response with Cosentyx 75 mg was 28%, which was not significantly better than the placebo group. ACR 50/70 responses were 17%/10% with Cosentyx 150 mg and 12%/5% with Cosentyx 75 mg which was not significantly different than placebo (9%/5%). The group treated with Orencia intravneous had significantly improved ACR 50/70 responses at Week 24 (28%/12%). Using as observed data, ACR

20/50/70 responses at Week 52 were 63%/46%/19% with Cosentyx 150 mg, 57%/26%/7% with Cosentyx 75 mg, and 75%/52%/23% with Orencia intravenous. There is a published Phase II dose-ranging study (n = 237) evaluating Cosentyx in rheumatoid arthritis.[8-10] The ACR 20 response at Week 16 (using last observation carried forward analysis) was 34%, 46.9%, 46.5%, 53.7% for the 25, 75, 150, and 300 mg doses vs. 36% for placebo; however, this did not achieve statistical significance. After Week 16, patients who responded to Cosentyx sustained their response through Week 52 with patients on the 150 mg dose having the greatest improvement over time (55% and 40% of patients with ACR 50 and ACR 70 responses, respectively, at Week 52). In another Phase II study, Cosentyx did not achieve higher ACR 20 response rates at Week 12 vs. placebo.[11] There was an open-label treatment period where ACR responses were generally maintained through Week 52. Some patients were treated with an intravenous formulation of secukinumab and generally responded similarly to those treated with Cosentyx. In another Phase II study, an intravenous formulation of secukinumab demonstrated limited efficacy in biologic-naïve patients with rheumatoid arthritis associated with the HLA-DRB1 allele.[12]

76. Uveitis. Efficacy is not established for this condition. There was not a statistically significant difference between Cosentyx SC and placebo in three Phase III studies that included patients with Behcet's uveitis (n = 118); active, noninfectious, non-Behcet's uveitis (n = 31); and quiescent, noninfectious, non-Behcet's uveitis (n = 125) [SHEILD, INSURE, and ENDURE studies, respectively].[13]

77. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	No changes to intent of clinical criteria. However, updated the examples of biologics a patients may have tried for psoriasis to include Siliq and Tremfya. Throughout the policy, changed references to Enbrel and Humira to etanercept and adalimumab product with Enbrel and Humira listed as examples of the respective products. Also, updated the Appendix to include all biologics approved since last review.	02/14/2018
Annual revision	Plaque Psoriasis: Add Cimzia and Ilumya to the list of therapies that the patient may have tried prior to Cosentyx.	02/27/2019
Annual revision	**Ankylosing Spondylitis:** Examples of a response to therapy were moved to a Note in the policy (previously listed as examples within the criteria). **Plaque Psoriasis:** For the exception applying to patients with a contraindication to methotrexate, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). Examples of biologics for psoriasis were moved to be included in the Appendix (previously listed in a Note in the criteria section). **Psoriatic Arthritis:** Examples of a response to therapy were moved to a Note in the policy (previously listed as examples within the criteria).	03/04/2020
Selected revision	**Non-Radiographic Axial Spondyloarthritis:** This newly approved indication was added to the policy. Criteria approve for initial therapy for 3 months if prescribed by a rheumatologist and the patient has objective signs of inflammation, defined as C-reactive protein elevated beyond the upper limit of normal for the reporting or laboratory sacroiliitis reported on magnetic resonance imaging. For patients currently taking Taltz, criteria approve for 3 years if the patient has responded to therapy. **Plaque psoriasis:** Examples of traditional systemic agent for psoriasis were moved to a Note (previously listed as examples within the criteria).	06/24/2020

APPENDIX

Biologic	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; ^ Off-label use of Kineret in JIA supported in guidelines.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Entyvio Intravenous Prior Authorization Policy

- Entyvio™ (vedolizumab intravenous injection – Takeda Pharmaceuticals America, Inc.)

REVIEW DATE: 08/26/2020

OVERVIEW

Entyvio, an integrin receptor antagonist, is indicated for the following uses:[1]

- **Crohn's disease**, in adults with moderately to severely active disease.
- **Ulcerative colitis**, in adults with moderately to severely active disease.

The product labeling states that Entyvio should be discontinued in patients who show no benefit by Week 14. In the pivotal studies evaluating Entyvio, all patients had previously tried corticosteroids and/or conventional agents for Crohn's disease and ulcerative colitis.

Guidelines

The American College of Gastroenterology (ACG) has updated guidelines (2018) for Crohn's disease. Entyvio is among the treatment recommendations for treatment of patients with moderate to severe disease or moderate to high risk disease (for induction of remission as well as maintenance of this remission).[2] Updated ACG guidelines for ulcerative colitis (2019) note that the following agents can be used for induction of remission in moderately to severely active disease: Uceris (budesonide extended-release tablets); oral or intravenous systemic corticosteroids, Entyvio, Xeljanz, or tumor necrosis factor inhibitors (adalimumab, Simponi SC, infliximab).[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Entyvio. All approvals are provided for the duration listed below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Entyvio as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Entyvio to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Entyvio is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Crohn's Disease.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **C)** Initial Therapy. Approve for 14 weeks if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient meets ONE of the following (a or b):
       1. Patient has tried or is currently taking systemic corticosteroids, or corticosteroids are contraindicated in this patient; OR
       2. Patient has tried one conventional systemic therapy for Crohn's disease; AND
          Note: Examples include azathioprine, 6-mercaptopurine, or methotrexate. An exception to the requirement for a trial of or contraindication to steroids or a trial of one other conventional systemic agent can be made if the patient has already tried at least one biologic. Refer to Appendix for examples of biologics used for Crohn's disease. These patients who have already received a biologic are not required to "step back" and try another agent.
     - **iii.** The medication is prescribed by or in consultation with a gastroenterologist.
   - **D)** Patient is Currently Receiving Entyvio. Approve for 1 year if the patient has had a response to therapy, as determined by the prescriber.

2. **Ulcerative Colitis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 14 weeks if the patients meets ALL of the following (i, ii, and iii):
     - **a)** Patient is ≥ 18 years of age; AND
     - **b)** Patient has had a trial of ONE systemic agent for ulcerative colitis; AND

Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone, methylprednisolone. A trial of a biologic also counts as a trial of one systemic agent for UC. Refer to Appendix for examples of biologics used for ulcerative colitis.

c) The medication is prescribed by or in consultation with a gastroenterologist.

B) Patient is Currently Receiving Entyvio. Approve for 1 year if the patient has had a response to therapy, as determined by the prescriber.

Note: Examples of a response to therapy include decreased stool frequency or rectal bleeding.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Entyvio is not recommended in the following situations:

1. **Concurrent Use with Other Biologics or with Targeted Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs) used for an Inflammatory Condition.** Entyvio should not be used in combination with tumor necrosis factor inhibitors or with Tysabri due to increased risk of infections.[1] There is also a increased risk of progressive multifocal leukoencephalopathy if used in combination with Tysabri. Combination therapy with other biologics or with targeted synthetic DMARDs used to treat inflammatory conditions (see Appendix for examples) is generally not recommended due to a potential for a higher rate of adverse effects with combinations and lack of data supportive of additive efficacy.

   Note: This does NOT exclude the use of conventional immunosuppressants (e.g., 6-mercaptopurine, azathioprine) in combination with Entyvio.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	**Ulcerative colitis** Change criteria to require a 2-month trial of at least one systemic agent, unless intolerant. Add a note stating that a trial of a biologic counts toward this requirement. (Previously, criteria specifically required a 2-month trial of a tumor necrosis factor inhibitor. **Crohn's disease:** Change criteria to require previous trial of corticosteroids (or is currently taking or contraindicated) or a conventional systemic agents. Add a note stating that a trial of a biologic counts toward this requirement of a trial of a previous agent. Previously, criteria specifically required a trial of a tumor necrosis factor inhibitor.	08/29/2018
Selected revision	**Ulcerative Colitis:** For the requirement that another agent be tried prior to Entyvio, remove the requirement that the trial is a duration of at least 2 months (not supported in updated guidelines).	03/27/2019
Early annual revision	**Crohn's Disease:** Move the requirement that the patient is an adult into the criteria section for initial therapy. Clarify criteria to require the patient be an adult ≥ 18	07/31/2019

	years of age. Previously, the requirement that the patient was an adult was listed as part of the diagnosis (i.e., previously listed as Crohn's disease in an adult) and applied to initial and continuation of therapy. **Ulcerative Colitis:** Move the requirement that the patient is an adult into the criteria section for initial therapy. Clarify criteria to require the patient be an adult ≥ 18 years of age. Previously, the requirement that the patient was an adult was listed as part of the diagnosis (i.e., previously listed as ulcerative colitis in an adult) and applied to initial and continuation of therapy. Since a specific duration of therapy is no longer required for patients who have tried another agent for ulcerative colitis, remove the exception for those who are intolerant.	
Annual revision	**Crohn's Disease:** Examples of biologics for Crohn's disease were moved to be included in the Appendix (previously listed in a Note in the criteria section). For the criterion applying to patients currently receiving Entyvio who have responded, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). **Ulcerative Colitis:** Examples of biologics for ulcerative colitis were moved to be included in the Appendix (previously listed in a Note in the criteria section). For the criterion applying to a patient currently receiving Entyvio who has responded, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). Examples of a response to therapy were moved to a Note in the policy (previously listed as examples within the criteria).	08/26/2020

APPENDIX

Product	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO, PsA
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; ^ Off-label use of Kineret in JIA supported in guidelines.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Etanercept Products Prior Authorization Policy

- Enbrel® (etanercept subcutaneous injection – Immunex/Amgen)

REVIEW DATE: 12/02/2020

OVERVIEW

Etanercept products tumor necrosis factor inhibitors (TNFis) approved for the following uses:[1]

- **Ankylosing spondylitis**, for reducing signs and symptoms in patients with active disease.
- **Juvenile idiopathic arthritis**, for reducing the signs and symptoms of moderate or severe active polyarticular disease in patients aged ≥ 2 years.
- **Plaque psoriasis**, for treatment patients 4 years of age or older with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

- **Psoriatic arthritis**, ± methotrexate for reducing the signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis.
- **Rheumatoid arthritis**, ± methotrexate for reducing the signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderate or severe active disease.

Guidelines

TNFis feature prominently in guidelines for treatment of inflammatory conditions.

- **Spondyloarthritis:** Guidelines for ankylosing spondylitis and nonradiographic axial spondylitis are published by the American College of Rheumatology (ACR)/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (2019).[5] TNFis are recommended for the initial biologic. In those who are secondary nonresponders to a TNFi, a second TNFi is recommended over switching out of the class.
- **Juvenile Idiopathic Arthritis (JIA):** There are guidelines from the ACR/Arthritis Foundation for the treatment of JIA (2019) specific to juvenile non-systemic polyarthritis, sacroiliitis, and enthesitis.[3] TNFis are the biologics recommended for polyarthritis, sacroiliitis, enthesitis. Actemra® (tocilizumab intravenous, tocilizumab subcutaneous) and Orencia® (abatacept intravenous, abatacept intravenous) are also among the biologics recommended for polyarthritis. Biologics are recommended following other therapies (e.g., following DMARDs for active polyarthritis or following a nonsteroidal anti-inflammatory drug [NSAID] for active JIA with sacroiliitis or enthesitis). However, there are situations where initial therapy with a biologic may be preferred over other conventional therapies (e.g., if there is involvement of high-risk joints such as the cervical spine, wrist, or hip; high disease activity; and/or those judged to be at high risk of disabling joint damage). TNFis may also be used as second- or third-line treatment for systemic JIA.[4]
- **Plaque Psoriasis:** Guidelines from the American Academy of Dermatologists (AAD) and National Psoriasis Foundation (NPF) [2019] recommend etanercept as a monotherapy treatment option for adults with moderate to severe disease.[7]
- **Psoriatic Arthritis:** Guidelines from ACR (2019) recommend TNFis over other biologics for use in treatment-naïve patients with PsA and in those who were previously treated with an oral therapy.[8]
- **Rheumatoid Arthritis:** Guidelines from ACR (2015) have TNFis and non-TNF biologics, administered ± methotrexate, equally positioned as a recommended therapy following a trial of a conventional synthetic DMARD (e.g., methotrexate, leflunomide, hydroxychloroquine, sulfasalazine).[2]

Other Uses with Supportive Evidence

There are guidelines and/or published data supporting the use of etanercept products in the following conditions:

- **Behcet's Disease:** The European Union Against Rheumatism (EULAR) recommendations (2018) include TNFis for initial or recurrent sight-threatening uveitis.[9] For patients refractory to first-line treatments (e.g., corticosteroids), TNFis are among the treatment options for mucocutaneous manifestations, venous thrombosis, severe or refractory gastrointestinal disease, and recurrent/chronic joint involvement. Recommendations for the use of TNFis in ocular inflammatory disorders from the American Academy of Ophthalmology (AAO) [2014] note that TNFis may be used first-line in patients with ophthalmic manifestations of Behcet's disease and for acute exacerbations of pre-existing Behcet's disease.[8] In particular, the monoclonal antibodies (adalimumab or infliximab products) are recommended for vision-threatening ocular manifestations of Behcet's disease.

- **Graft versus Host Disease:** Guidelines for hematopoietic cell transplantation from the National Comprehensive Cancer network (NCCN) [version 2.2020 – March 23, 2020] list etanercept among the agents used for steroid-refractory disease.[46]
- **Ocular Inflammatory Disorders:** The American Academy of Ophthalmology (AAO) [2014] note that adalimumab may be used in patients with uveitis due to various causes (e.g., spondyloarthropathy-associated or human leukocyte antigen [HLA]-B27-associated uveitis, JIA-associated uveitis, and other posterior uveitides and panuveitis syndromes).[8] TNFis should be considered second-line in vision-threatening JIA-associated uveitis when methotrexate has failed or is not tolerated (strong recommendation) and may be used as corticosteroid-sparing treatment for vision-threatening chronic uveitis from seronegative spondyloarthropathy (strong recommendation). TNFis may also be considered in other patients who have vision-threatening or corticosteroid-dependent disease who have failed first-line therapies and as a second-line immunomodulatory agent for severe ocular inflammatory conditions (including chronic and severe scleritis).
- **Pyoderma Gangrenosum:** Although guidelines are not current, multiple topical and systemic therapies have been used for pyoderma gangrenosum. Oral prednisone is the most common initial immunosuppressant medication.[10-13] Other systemic therapies include cyclosporine, methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, and TNFis (i.e., infliximab, etanercept, and adalimumab products). In case reports, TNFis have been effective.
- **Still's Disease:** There are not current guidelines for treatment of Still's disease. However, it presents in adults with features similar to those of systemic onset JIA.[24] In addition, there is a small trial which demonstrated efficacy of etanercept used for this condition.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of etanercept products. Because of the specialized skills required for evaluation and diagnosis of patients as well as the monitoring required for adverse events and long-term efficacy, initial approval requires etanercept products to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of etanercept products is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Ankylosing Spondylitis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if prescribed by or in consultation with a rheumatologist.
   - **B)** Patient is Currently Receiving an Etanercept Product. Approve for 3 years if the patient had a response, as determined by the prescriber.
     Note: Examples of a response to therapy include decreased pain or stiffness, or improvement in function or activities of daily living. Patient may not have a full response but there should be some response.

2. **Juvenile Idiopathic Arthritis (JIA) [or Juvenile Rheumatoid Arthritis] (regardless of type of onset).** Approve for the duration noted if the patient meets ONE of the following (A or B):
   Note: This includes a patient with juvenile spondyloarthropathy/active sacroiliac arthritis.
   - **H)** Initial Therapy. Approve for 3 months if the patient meets BOTH of the following criteria (i and ii):
     - **i.** Patient meets one of the following conditions (a, b, c, or d):
       - **i)** Patient has tried one other systemic therapy for this condition; OR
         Note: Examples of other systemic therapy for JIA include methotrexate, sulfasalazine, or leflunomide, a nonsteroidal anti-inflammatory drug (NSAID) [e.g., ibuprofen, naproxen]. A previous trial of a biologic also counts as a trial of one agent for JIA. Refer to Appendix for examples of biologics used for JIA.
       - **j)** Patient will be starting on therapy concurrently with methotrexate, sulfasalazine, or leflunomide; OR
       - **k)** Patient has an absolute contraindication to methotrexate, sulfasalazine, or leflunomide; OR
         Note: Examples of contraindications to methotrexate include pregnancy, breast feeding, alcoholic liver disease, immunodeficiency syndrome, blood dyscrasias.
       - **l)** Patient has aggressive disease, as determined by the prescriber; AND
     - **ii.** The medication is prescribed by or in consultation with a rheumatologist.
   - **B)** Patient is Currently Receiving an Etanercept Product. Approve for 3 years if the patient had a response, as determined by the prescriber.
     Note: Examples of a response include improvement in limitation of motion, less joint pain or tenderness, decreased duration of morning stiffness or fatigue, improved function or activities of daily living, reduced dosage of corticosteroids. Patient may not have a full response but there should be some response.

3. **Plaque Psoriasis**. Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient is ≥ 4 years of age; AND
     - **ii.** Patient meets one of the following conditions (a or b):
       - **a)** Patient has tried at least at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR
         Note: Examples include methotrexate, cyclosporine, acitretin, or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already has a 3-month trial or previous intolerance to at least one biologic. Refer to Appendix for examples of biologics used for psoriasis. A patient who has already tried a biologic for psoriasis is not required to "step back" and try a traditional systemic agent for psoriasis.

b) Patient has a contraindication to methotrexate, as determined by the prescriber; AND

iii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving an Etanercept Product. Approve for 3 years if the patient had a response, as determined by the prescriber.
Note: Patient may not have a full response but there should be some response.

4. Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the agent is prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving an Etanercept Product. Approve for 3 years if the patient had a response, as determined by the prescriber.
Note: Examples of a response include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improvements in acute phase reactants [for example, C-reactive protein [CRP]). Patient may not have a full response but there should be some response.

5. Rheumatoid Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (i and ii):

i. Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND
Note: Examples include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already has a 3-month trial at least one biologic. Refer to Appendix for examples of biologics used for rheumatoid arthritis. A patient who has already tried a biologic for rheumatoid arthritis is not required to "step back" and try a conventional synthetic DMARD.

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving an Etanercept Product. Approve for 3 years if the patient had a response, as determined by the prescriber.
Note: Examples of a response include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids. Patient may not have a full response but there should be some response.

Other Uses with Supportive Evidence

6. Behcet's Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ONE of the following (i or ii):

i. Patient has tried at least one conventional therapy; OR
Note: Examples include systemic corticosteroids (e.g., methylprednisolone), immunosuppressants (e.g., azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, tacrolimus, Leukeran® [chlorambucil], cyclophosphamide, interferon alfa). An exception to the requirement for a trial of one conventional therapy can be made if the patient has already had a trial of at least one tumor necrosis factor inhibitor (e.g., an adalimumab or infliximab product). A patient who has already tried a biologic for Behcet's disease is not required to "step back" and try a conventional therapy.

ii. The medication is prescribed by or in consultation with a rheumatologist, dermatologist, ophthalmologist, gastroenterologist, or neurologist.

B) Patient is Currently Receiving an Etanercept Product. Approve for 1 year if the patient has responded to therapy, as determined by the prescriber.

Note: Patient may not have a full response but there should be some response.

7. **Graft-Versus-Host Disease.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   A) Initial Therapy. Approve for 1 month if the patient meets BOTH of the following (i and ii):
      i. Patient has tried at least one conventional systemic treatment for graft-versus-host disease; AND
      Note: Examples of conventional systemic treatments include systemic corticosteroids (e.g., methylprednisolone), antithymocyte globulin, cyclosporine, tacrolimus, and mycophenolate mofetil.
      ii. The medication is prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center.
   B) Patient is Currently Receiving an Etanercept Product. Approve for 3 months if the patient had a response, as determined by the prescriber.

8. **Pyoderma Gangrenosum.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   A) Initial Therapy. Approve for 4 months if the patient meets BOTH of the following (i and ii):
      14 Patient meets ONE of the following (a or b):
         a) Patient has tried one systemic corticosteroid; OR
         Note: An example is prednisone.
         b) Patient has tried one other immunosuppressant for at least 2 months or was intolerant to one of these agents; AND
         Note: Examples include mycophenolate mofetil and cyclosporine.
      15 The medication is prescribed by or in consultation with a dermatologist.
   B) Patient is Currently Receiving an Etanercept Product. Approve for 1 year if the patient had a response, as determined by the prescriber.
      Note: Patient may not a full response, but there should some response.

9. **Scleritis or Sterile Corneal Ulceration.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (i and ii):
      14 Patient has tried one other therapy for this condition; AND
      Note: Examples include oral nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin, naproxen, or ibuprofen; oral, topical (ophthalmic) or intravenous corticosteroids (such as prednisone, prednisolone, methylprednisolone); methotrexate; cyclosporine; or other immunosupressants.
      15 The medication is prescribed by or in consultation with an ophthalmologist.
   B) Patient is Currently Receiving an Etanercept Product. Approve for 1 year if the patient had a response, as determined by the prescriber.
      Note: Examples of a response to therapy include decreased inflammation, reduced use of steroids or immunomodulators, decreased eye pain, redness, and/or photophobia. Patient may not have a full response but there should be some response.

10. Spondyloarthritis, Other Subtypes. Approve for the duration noted if the patient meets ONE of the following (A or B):

Note: This includes undifferentiated arthritis, non-radiographic axial SpA, Reactive Arthritis (Reiter's disease). For Ankylosing Spondylitis or Psoriatic Arthritis, refer to the respective criteria under FDA-approved indications].

C) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (i and ii):

i. Patient meets ONE of the following conditions (a or b):

a) Patient has arthritis primarily in the knees, ankles, elbows, wrists, hands, and/or feet AND has tried at least ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) has been tried; OR

Note: Examples include methotrexate, leflunomide, sulfasalazine.

b) Patient has axial spondyloarthritis AND has objective signs of inflammation, defined as at least one of the following [(1) or (2)]:

a. C-reactive protein (CRP) elevated beyond the upper limit of normal for the reporting laboratory; OR

b. Sacroiliitis reported on magnetic resonance imaging (MRI); AND

ii. The medication is prescribed by or in consultation with a rheumatologist.

D) Patient is Currently Receiving an Etanercept Product. Approve for 1 year if the patient had a response, as determined by the prescriber.

Note: Examples of a response include decreased pain or stiffness, improved function or activities of daily living. Patient may not have a full response but there should be some response.

11. Still's Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, and iii):

~~14~~ Patient has tried one corticosteroid; AND

~~15~~ Patient has tried one conventional synthetic disease-modifying antirheumatic drug (DMARD) given for at least 2 months or was intolerant; AND

Note: An example is methotrexate.

16 The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving an Etanercept Product. Approve for 1 year if the patient had a response, as determined by the prescriber.

Note: Patient may not have a full response but there should be some response.

12. Uveitis (including other posterior uveitides and panuveitis syndromes). Approve for the duration noted if the patient meets the ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (i and ii):

14 The patient has tried one of the following therapies for this condition: periocular, intraocular, or systemic corticosteroids or immunosuppressives; AND

Note: Examples of corticosteroids include prednisolone, triamcinolone, betamethasone, methylprednisolone, and prednisone. Examples of immunosuppressives include methotrexate, mycophenolate mofetil, azathioprine, and cyclosporine. An exception to the requirement for a trial of one of these therapies can be made if the patient has already tried an adalimumab or infliximab product for uveitis. A patient who has already tried a biologic for uveitis is not required to try another therapy.

15 The medication is prescribed by or in consultation with an ophthalmologist.

B) Patient is Currently Receiving an Etanercept Product. Approve for 1 year if the patient had a response, as determined by the prescriber.

Note: Examples of a response include decreased inflammation, reduced use of steroids or immunomodulators, and improvement in visual acuity. Patient may not have a full response but there should be some response.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of etanercept products is not recommended in the following situations:

1. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Etanercept products should not be administered in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see Appendix for examples). Combination therapy is generally not recommended due to a higher rate of AEs with combinations and lack of data supportive of additional efficacy.
   Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with etanercept products.

2. **Crohn's Disease.** In a double-blind, placebo-controlled trial etanercept (Enbrel) was not effective for the treatment of moderate to severe Crohn's disease.[25] However, arthritis (spondyloarthropathy, ankylosing spondylitis) may be associated with Crohn's disease and etanercept products may be effective for spondyloarthropathy in these patients.[26]

3. **Inflammatory Myopathies (Polymyositis, Dermatomyositis, Inclusion Body Myositis).** Information is conflicting. In one retrospective review of eight patients with either dermatomyositis or polymyositis some patients responded (improved motor strength and decreased fatigue) to treatment with an etanercept product.[27] In this case series, an etanercept product was added on to treatment with corticosteroids, intravenous immunoglobulin (IVIG), and DMARDs; there were no standardized outcome measures. In another case series in patients (n = 5) with dermatomyositis who had not responded to steroids and cytotoxic therapy (methotrexate, azathioprine, cyclosporine), the cytotoxic drugs were discontinued and etanercept was given for at least 3 months.[28] All patients had exacerbation of disease and etanercept was stopped. In a 1-year, double-blind study, patients were randomized to receive etanercept 50 mg weekly (n = 11) or placebo (n = 5).[29] All patients who received placebo were judged as treatment failures whereas five patients in the etanercept group were successfully weaned off of prednisone. More studies are needed demonstrating the efficacy of etanercept and its long-term effects.[30] In a 6-month, open-label study of etanercept in patients with refractory juvenile dermatomyositis (n = 9), minimal improvement was noted in disease activity with some patients experiencing worsening disease.[31]

4. **Hidradenitis Suppurativa.** A prospective, randomized, double-blind, placebo-controlled study assigned patients (n = 20) to treatment with etanercept 50 mg twice weekly or placebo for 12 weeks.[32] Following 12 weeks of treatment, all patients received open-label etanercept for an additional 12 weeks. The study found no statistically significant difference between etanercept 50 mg twice weekly and placebo among physician global assessment, patient global assessment, and the Dermatology Life Quality Index (DLQI) at Week 12 or Week 24. A systematic review (2013) extracted data from case reports and RCTs and recommended against the use of etanercept for treatment of hidradenitis suppurativa.[33]

5. **Polymyalgia Rheumatica (PMR).** ACR/EULAR guidelines for the management of PMR (2015) strongly recommend against the use of TNFis for treatment of PMR.[34] This recommendation is based on lack of evidence for benefit as well as considerable potential for potential harm. While etanercept has been evaluated in small numbers of patients with PMR, efficacy has not been established.[35-37]

6. **Sarcoidosis.** Evidence does not support use of etanercept in ocular or pulmonary disease. Recommendations for the use of TNFis in ocular inflammatory disorders from the AAO (2014) note that infliximab or adalimumab may be considered as second-line immunomodulatory therapy for patients failing or intolerant of standard immunomodulatory agents.[8] A discretionary recommendation (indicating trade-offs are less certain) is that etanercept should not be used in the treatment of ocular

sarcoidosis (moderate-quality evidence). In a double-blind study patients (n = 18) with chronic ocular sarcoidosis and ongoing inflammation were randomized to etanercept or placebo for 6 months.[38] Patients had received ≥ 6 months of therapy with methotrexate and were currently on corticosteroids. For most of the patients, therapy with etanercept was not associated with significant improvement. In a prospective, open-label trial in patients with Stage II or III progressive pulmonary sarcoidosis, treatment with etanercept was frequently associated with early or late treatment failure.[39] This trial was ended early because an excessive number of patients (n = 11/17) had disease progression on etanercept. Recommendations for best practice in the management of pulmonary and systemic sarcoidosis mention infliximab and adalimumab as therapeutic options for management of disease.[40]

7. **Large Vessel Vasculitis (e.g., Giant Cell Arteritis, Takayasu's Arteritis).** Guidelines from EULAR for the management of large vessel vasculitis (e.g., giant cell arteritis, Takayasu's arteritis) do not mention the use of TNFis.[41] Additionally, a meta-analysis of RCTs did not find evidence supporting remission or reduction of corticosteroid dose with the use of TNFis in large vessel vasculitis.[42] In a double-blind trial patients with biopsy proven giant cell arteritis with AEs due to corticosteroids were randomized to etanercept 25 mg twice weekly (n = 8) or placebo (n = 9) for 12 months.[43] Corticosteroids were continued but were reduced if possible according to a predefined protocol. The primary outcome was the ability to withdraw the corticosteroid therapy and control disease activity at 12 months. After 12 months, there was not a statistically significant difference in the proportion of patients able to control disease without corticosteroid therapy with etanercept (50%) vs. placebo (22.2%). However, patients on etanercept had a significantly lower dose of accumulated prednisone during the first year of treatment (P = 0.03). In a retrospective single center study in patients with refractory Takayasu's arteritis (n = 25), patients were treated with infliximab (n = 21) or etanercept (n = 9).[44] Five patients who were initially treated with etanercept were switched to infliximab. Therapy with TNFis was associated with remission in many patients and dose reduction or discontinuation of prednisone and other immunosuppressant therapies. A randomized controlled trial is needed to better define the efficacy and safety of etanercept.

8. **Wegener's Granulomatosis.** Etanercept is not effective in the induction or maintenance of disease remissions in patients with Wegener's. In a double-blind trial, 180 patients with active Wegener's granulomatosis were randomized to etanercept or placebo in combination with standard therapies (e.g., cyclophosphamide, methotrexate, corticosteroids) depending on disease severity.[45] When remission was achieved, standard medications were tapered according to protocol guidelines. Patients were enrolled over 28 months and the mean follow-up was 27 months. Of the 174 patients who were evaluable, 126 patients (72.4%) achieved sustained remissions, but only 86 patients overall (49.4%) maintained their disease remissions throughout the trial. There were no differences between etanercept and the control group in the percent of patients achieving sustained remissions (69.7% vs. 75.3%, P = 0.39); in the percent of patients with sustained periods of low disease activity (86.5% vs. 90.6%); or time to achieve these outcomes. Disease flares were common in both groups. AEs were frequent and often severe. During the study, 56.2% of patients on etanercept and 57.1% on placebo had at least one severe or life-threatening adverse event or died. Six of the etanercept patients and none of the controls developed solid malignancies. Use of etanercept in patients with Wegener's granulomatosis who are receiving immunosuppressant drugs is not recommended.[1]

9. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Patients Established on Enbrel:** Remove this criterion for patients currently established on therapy for ≥ 90 days. Patients currently taking an etanercept product are now addressed in the criteria section for each specific indication. • Add a requirement that the patient must have responded to initial therapy for the following indications: Behcet's disease, Graft-Versus-Host Disease, pyoderma gangrenosum, scleritis or sterile corneal ulcerations, Still's disease, Spondyloarthritis, and uveitis. **Previous Therapies:** For these indications, add the following agents to the list of therapies the patient may have tried prior to etanercept: • Plaque Psoriasis: Cimzia, Ilumya • Juvenile Idiopathic Arthritis: Actemra subcutaneous **Behcet's disease:** Modify criteria to change previous therapy from biologic to more specifically say tumor necrosis factor inhibitor. **Conditions Not Recommended for Coverage:** Ocular and Pulmonary Sarcoidosis were combined into one condition (Sarcoidosis) which is not recommended for coverage. **Other:** Policy name was changed to Inflammatory Conditions – Etanercept Products. Throughout the policy, references to Enbrel were reworded to say etanercept products.	11/07/2018
Selected Revision	**Spondyloarthritis, Other Subtypes:** This off-label approval condition was reworded (previously listed as Spondyloarthritis, Subtypes Other than Ankylosing Spondylitis or Psoriatic Arthritis). There is a note which directs to criteria for FDA-approved subtypes of	04/24/2019

	Spondyloarthritis (Ankylosing Spondylitis, Psoriatic Arthritis). Criteria were changed to approve for 3 months for patients starting therapy (previously was 1 year). For patients with primarily axial disease, a criterion was added to require objective signs of inflammation, defined as C-reactive protein (CRP) elevated beyond the upper limit of normal for the reporting laboratory or sacroiliitis reported on magnetic resonance imaging. For patients currently receiving therapy, examples of a response to therapy were added; the requirement that patients be on an etanercept product for ≥ 90 days was removed.	
Annual Revision	**Juvenile Idiopathic Arthritis:** For the exception applying to patients with aggressive disease, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). **Plaque Psoriasis:** For the exception applying to patients with a contraindication to methotrexate, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). Skyrizi was added to the list of biologics that the patient may have tried prior to etanercept. **Behcet's Disease:** To align with other policies that approve for this condition, the duration of the initial approval was changed to 3 months (previously was 1 year). For patients currently receiving therapy, the requirement that patients be on an etanercept product for ≥ 90 days was removed. **Graft-Versus-Host Disease:** To align with other policies that approve for this condition, the duration of the initial approval was changed to 1 month and the duration of approval for patients currently taking etanercept was changed to 3 months (previously was 1 year for all patients). For patients currently receiving therapy, the requirement that patients be on an etanercept product for ≥ 90 days was removed. **Pyoderma Gangrenosum:** To align with the other policies that approve for this condition, the duration of the initial approval was changed to 4 months (previously was 1 year). For patients currently receiving therapy, the requirement that patients be on an etanercept product for ≥ 90 days was removed. **Scleritis/Sterile Corneal Ulceration:** To align with other policies that approve for this condition, the duration of the initial approval was changed to 3 months (previously was 1 year). For patients currently receiving therapy, the requirement that patients be on an etanercept product for ≥ 90 days was removed. **Still's Disease:** To align with other policies that approve for this condition, the duration of the initial approval was changed to 3 months (previously was 1 year). For patients currently receiving therapy, the requirement that patients be on an etanercept product for ≥ 90 days was removed. **Uveitis:** To align with other policies that approve for this condition, the duration of the initial approval was changed to 3 months (previously was 1 year). For patients currently receiving therapy, the requirement that patients be on an etanercept product for ≥ 90 days was removed.	11/06/2019
Annual Revision	**Juvenile Idiopathic Arthritis:** For the criterion applying to previous therapy, wording was changed to specify this must have been a systemic therapy (criteria previously required a trial of one other agent, with systemic therapies listed among the examples). Examples of biologics were moved to be included in the Appendix (previously listed in a Note in the criteria section). **Plaque Psoriasis:** Examples of biologics were moved to be included in the Appendix (previously listed in a Note in the criteria section). **Rheumatoid Arthritis:** Examples of biologics were moved to be included in the Appendix (previously listed in a Note in the criteria section). **Graft-Versus-Host Disease:** To align with updated NCCN guidelines and other policies, criteria were changed to require at least one conventional systemic treatment prior to an etanercept product. Previously, criteria required that the patient had tried at least one other immunosuprressant or be concurrently receiving an immunosuppressant in combination with an etanercept product.	12/02/2020

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of JAK pathways	RA
Xeljanz® (tofacitinib tablets)	Inhibition of JAK pathways	RA, PJIA, PsA, UC
Xeljanz® XR (tofacitinib extended-release tablets)	Inhibition of JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; ^ Off-label use of Kineret in JIA supported in guidelines; DMARDs – Disease-modifying antirheumatic drug.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Ilaris Prior Authorization Policy

- Ilaris® (canakinumab for subcutaneous injection – Novartis)

REVIEW DATE: 04/22/2020; selected revision 06/24/2020

OVERVIEW

Ilaris, an interleukin-1β (IL-1β) blocker, is indicated for the following uses:[1]

- **Cryopyrin-Associated Periodic Syndromes** (CAPS), including Familial Cold Autoinflammatory Syndrome and Muckle-Wells Syndrome, for treatment of patients who are ≥ 4 years of age.
- **Still's Disease**, including Active **adult-onset Still's Disease** and **systemic juvenile idiopathic arthritis** (SJIA), in patients ≥ 2 years of age.
- **Tumor necrosis factor receptor associated periodic syndrome** (TRAPS), in adult and pediatric patients.

- **Hyperimmunoglobulin D Syndrome/mevalonate kinase deficiency**, in adult and pediatric patients.
- **Familial Mediterranean Fever**, in adult and pediatric patients.

In the pivotal study for period fevers (TRAPS, Hyperimmunoglobulin D Syndrome/mevalonate kinase deficiency, and Familial Mediterranean Fever), patients were assessed for a response following 4 months of treatment with Ilaris.

Guidelines

Ilaris is used for a variety of periodic fever syndromes and inflammatory conditions.

- **SJIA:** There are standardized treatment plans published for use of Ilaris.[7,8] At Month 3, patients with unchanged or worsening disease or patients whose steroid dose is > 50% of the starting dose should have an increase in prednisone plus either addition of methotrexate or change to Actemra. Guidelines from the American College of Rheumatology for the management of SJIA (2013) mention Ilaris as a treatment alternative, depending upon the manifestations of SJIA being treated.[9] While there are a number of other effective options for treating synovitis in patients with active SJIA, effective options for treatment of macrophage activation syndrome are much more limited and include Kineret (anakinra subcutaneous injection), calcineurin inhibitors, and systemic corticosteroids (no preferential sequencing noted). Although use of Ilaris is uncertain in some situations, macrophage activation syndrome is a potentially life-threatening situation with limited treatment options.
- **TRAPS:** European guidelines for autoinflammatory disorders (2015) note that IL-1 blockade is beneficial for the majority of patients; maintenance with IL-1 blockade, which may limit corticosteroid exposure, may be used in patients with frequent attacks and/or subclinical inflammation between attacks.
- **Mevalonate Kinase Deficiency:** European guidelines for autoinflammatory disorders (2015) recommend consideration of short-term use of IL-1 blockers for termination of attacks and to limit or prevent steroid adverse events.[5] Maintenance therapy with an IL-1 blocker may be used in patients with mevalonate kinase deficiency and frequent attacks and/or subclinical inflammation between attacks.
- **Familial Mediterranean Fever:** Guidelines for familial Mediterranean fever from the European League Against Rheumatism (EULAR) [2016] note that treatment goals are to prevent the clinical attacks and to suppress chronic subclinical inflammation.[6] IL-1 blockade is an option for patients with protracted febrile myalgia. In patients who develop AA amyloidosis, the maximal tolerated dose of colchicine and biologics (especially IL-1 blockade) are recommended.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Ilaris. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ilaris as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Ilaris to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

All reviews for use of Ilaris for COVID-19 and/or cytokine release syndrome associated with COVID-19 will be forwarded to the Medical Director.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Ilaris is recommended in those who meet the following criteria:

FDA-Approved Indications

3. **Cryopyrin-Associated Periodic Syndromes (CAPS) [including Familial Cold Autoinflammatory Syndrome, Muckle-Wells Syndrome, and Neonatal Onset Multisystem Inflammatory Disease {NOMID} or Chronic Infantile Neurological Cutaneous and Articular {CINCA} Syndrome].** Approve for the duration noted if the patient meets ONE of the following (A or B):
   4. Initial Therapy. Approve for 3 months if the patient meets the following conditions (i and ii):
      i. Patient is ≥ 4 years of age; AND
      ii. Ilaris is prescribed by or in consultation with a rheumatologist, geneticist, allergist/immunologist, or dermatologist.
   5. Patient is Currently Receiving Ilaris. Approve for 3 years if the patient has had a response, as determined by the prescriber.

6. **Familial Mediterranean Fever.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   A) Initial Therapy. Approve for 4 months if prescribed by or in consultation with a rheumatologist, nephrologist, geneticist, gastroenterologist, oncologist, or hematologist.
   B) Patient is Currently Receiving Ilaris. Approve for 3 years if the patient has had a response, as determined by the prescriber.
   Note: The patient may not have a full response, but there should have been a recent or past response to Ilaris.

3. **Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   A) Initial Therapy. Approve for 4 months if Ilaris is prescribed by or in consultation with a rheumatologist, nephrologist, geneticist, oncologist, or hematologist.
   B) Patient is Currently Receiving Ilaris. Approve for 3 years if the patient has had a response, as determined by the prescriber.
   Note: The patient may not have a full response, but there should have been a recent or past response to Ilaris.

4. **Systemic Juvenile Idiopathic Arthritis (SJIA).** Approve for the duration noted if the patient meets ONE of the following (A or B):
   A) Initial Therapy. Approve for 3 months (which is adequate for three doses) if the patient meets ALL of the following conditions (i, ii, and iii):
      i. Patient is ≥ 2 years of age; AND
      ii. Patient meets ONE of the following conditions (a, b, or c):
         a) Patient has tried at least TWO other biologics; OR
         Note: Examples of biologics for SJIA include Actemra (tocilizumab intravenous infusion, tocilizumab subcutaneous injection), Kineret (anakinra subcutaneous injection), Orencia (abatacept intravenous infusion, abatacept subcutaneous injection), an etanercept product, adalimumab product, or infliximab product.
         b) Patient meets BOTH of the following [(1) and (2)]:
            (1) Patient has features of poor prognosis, as determined by the prescriber; AND
            Note: Examples of features of poor prognosis include arthritis of the hip, radiographic damage, 6-month duration of significant active systemic disease, defined by: fever,

elevated inflammatory markers, or requirement for treatment with systemic glucocorticoids.

(2) Patient has tried Actemra or Kineret; OR

c) Patient meets BOTH of the following [(1) and (2)]:

(1) Patient has features of SJIA with active systemic features with concerns of progression to macrophage activation syndrome, as determined by the prescriber; AND

(2) Patient has tried Kineret; AND

iii. Ilaris is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Ilaris. Approve for 3 years if the patient has had a response as determined by the prescriber.

Note: Examples of responses to therapy include resolution of fevers or rash, improvement in limitation of motion, less joint pain or tenderness, decreased duration of morning stiffness or fatigue; improved function or activities of daily living, and reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Ilaris.

5. Stills Disease, Adult Onset. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months (which is adequate for three doses) if the patient meets ALL of the following conditions (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

Note: If the patient is < 18 years of age, refer to criteria for systemic juvenile idiopathic arthritis.

ii. Patient meets ONE of the following conditions (a, b, or c):

a) Patient has tried at least TWO other biologics; OR

Note: Examples of biologics include Actemra (tocilizumab intravenous infusion, tocilizumab subcutaneous injection), Kineret (anakinra subcutaneous injection), Orencia (abatacept intravenous infusion, abatacept subcutaneous injection), an etanercept product, adalimumab product, or infliximab product.

b) Patient meets BOTH of the following [(1) and (2)]:

(1) Patient has features of poor prognosis, as determined by the prescriber; AND

Note: Examples of features of poor prognosis include arthritis of the hip, radiographic damage, 6-month duration of significant active systemic disease, defined by: fever, elevated inflammatory markers, or requirement for treatment with systemic glucocorticoids.

(2) Patient has tried Actemra or Kineret; OR

c) Patient meets BOTH of the following [(1) and (2)]:

(1) Patient has active systemic features with concerns of progression to macrophage activation syndrome, as determined by the prescriber; AND

(2) Patient has tried Kineret; AND

iii. Ilaris is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Ilaris. Approve for 3 years if the patient has had a response as determined by the prescriber.

Note: Examples of responses to therapy include resolution of fevers or rash, improvement in limitation of motion, less joint pain or tenderness, decreased duration of morning stiffness or fatigue; improved function or activities of daily living, and reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Ilaris.

5. Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 4 months if prescribed by or in consultation with a rheumatologist, geneticist, nephrologist, oncologist, or hematologist.

B) Patient is Currently Receiving Ilaris. Approve for 3 years if the patient has had a response, as determined by the prescriber.
Note: The patient may not have a full response, but there should have been a recent or past response to Ilaris.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ilaris is not recommended in the following situations:

1. **Concurrent Biologic Therapy.** Ilaris has not been evaluated and should not be administered in combination with another biologic agent for an inflammatory condition (see Appendix for examples). An increased incidence of serious infections has been associated with another IL-1 blocker, Kineret, when given in combination with tumor necrosis factor inhibitor in patients with rheumatoid arthritis. Concomitant administration of Ilaris and other agents that block IL-1 or its receptors is not recommended.

2. **COVID-19 (Coronavirus Disease 2019).** Forward all requests to the Medical Director.
Note: This includes requests for cytokine release syndrome associated with COVID-19.

3. **Rheumatoid Arthritis.** Efficacy is not established.[11,12] In a 12-week, Phase II, placebo-controlled, double-blind study, 277 patients who had failed methotrexate were randomized to Ilaris or placebo.[11] Although the ACR 50 at Week 12 was higher for Ilaris 150 mg (given every 4 weeks) compared with placebo (26.5% vs. 11.4%, respectively; P = 0.028), there was not a statistically significant difference in ACR 50 for the other Ilaris treatment groups (Ilaris 300 mg every 2 weeks; Ilaris 600 mg loading dose followed by 300 mg every 2 weeks).

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	No criteria changes.	11/07/2018
Annual revision	No criteria changes.	11/06/2019
Selected revision	**COVID-19:** This indication (including use in cytokine release syndrome associated with COVID-19) was added to the policy as a Condition Not Recommended for Coverage. All reviews are directed to the Medical Director.	04/01/2020
Early annual revision	**Systemic Juvenile Idiopathic Arthritis:** For the exceptions applying to patients with a poor prognosis and for those with active systemic features and concerns of progression to macrophage activation syndrome, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician).	04/22/2020
06/24/2020	**Systemic Juvenile Idiopathic Arthritis:** Resolution of rash was added as an example of a response to therapy. **Still's Disease, Adult Onset:** Criteria were updated to align with the new labeling. Criteria for systemic juvenile idiopathic arthritis also apply to adult-onset Still's disease.	06/24/2020

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, PJIA, PsO, PsA, RA, SJIA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: PJIA, PSA, RA
		IV formulation: PJIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Ilaris (canakinumab SC injection**)**	Inhibition of IL-1β	SJIA
Kineret® (anakinra SC injection)	Inhibition of IL-1	RA, SJIA^
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA

Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; IV – Intravenous, TNF – Tumor necrosis factor; IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; PJIA – Polyarticular juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; SJIA – Systemic juvenile idiopathic arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial sponlyoarthritis; ^ Off-label use of SJIA supported in guidelines; DMARD – Disease-modifying antirheumatic drug.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Ilumya™ (tildrakizumab-asmn for subcutaneous injection – Sun Pharmaceuticals)

DATE REVIEWED: 04/22/2020

OVERVIEW

Ilumya is a humanized immunoglobulin G monoclonal antibody that binds to interleukin (IL)-23, a pro-inflammatory cytokine.[1] It binds to the p19 subunit of IL-23 and inhibits the intracellular and downstream signaling of IL-23 which is required for the terminal differentiation and survival of T helper 17 cells. Ilumya is indicated for treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. It is administered subcutaneously (SC) at Weeks 0 and 4 and then once every 12 weeks thereafter. Ilumya should be administered by a healthcare professional.

Disease Overview

Although the etiology of psoriasis is not fully established, abnormal keratin formation, epidermal proliferation, activation of the immune system, and hereditary factors appear to play roles in the pathogenesis of the disease. In psoriasis, levels of IL-23p40 and IL-12/23p40 messenger RNA are upregulated but decrease with treatment. By blocking the release of proinflammatory cytokines and chemokines, Ilumya has an inhibitory effect on the inflammatory process.

Guidelines

Joint guidelines from the American Academy of Dermatology and National Psoriasis Medical Board (2019) have been published for management of psoriasis with biologics.[2] These guidelines list Ilumya as a monotherapy treatment option for patients with moderate to severe plaque psoriasis. Guidelines from the European Dermatology Forum (2015) recommend biologics (i.e., etanercept, adalimumab, infliximab, Stelara SC) as second-line therapy for induction and long-term treatment if phototherapy and conventional systemic agents have failed, are contraindicated, or are not tolerated.[3]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Ilumya. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ilumya as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Ilumya to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ilumya is recommended in those who meet the following criteria:

I) Plaque Psoriasis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following criteria (i, ii, and iii):

i. The patient is ≥ 18 years of age; AND

ii. The patient meets ONE of the following conditions (a or b):

a) The patient has tried at least at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant.

Note: Examples of one traditional systemic agent include methotrexate [MTX], cyclosporine, acitretin tablets, or psoralen plus ultraviolet A light [PUVA]). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already had a 3-month trial or previous intolerance to at least one biologic. Refer to **Appendix** for examples of biologics used for plaque psoriasis. These patients who have already tried a biologic for psoriasis are not required to "step back" and try a traditional systemic agent for psoriasis); OR

b) The patient has a contraindication to methotrexate (MTX), as determined by the prescriber; AND

iii. Ilumya is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Ilumya. Approve for 3 years if the patient has responded, as determined by the prescriber.

Note: The patient may not have a full response, but there should have been a recent or past response to Ilumya.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Ilumya has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

78. Concurrent Use with other Biologics or with Targeted Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs). Data are lacking evaluating concomitant use of Ilumya with another biologic or with a targeted synthetic DMARD for an inflammatory condition (see **Appendix** for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMRADs has a potential for a higher rate of adverse effects and lack controlled trial data in support of additive efficacy.[4]

Note: This does NOT exclude the use of MTX (a traditional systemic agent used to treat psoriasis) in combination with Ilumya.

79. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	NA	03/21/2018
Annual revision	**Plaque Psoriasis:** Add Cimzia to the list of biologics which may have been tried prior to approval of Ilumya.	03/27/2019
Annual revision	**Plaque Psoriasis:** For the exception applying to patients with a contraindication to methotrexate, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). Examples of traditional systemic agents were moved to a Note in the criteria section. Examples of biologics for psoriasis were moved to be included in the Appendix (previously listed in a Note in the criteria section). Explanation that the patient may not have a full response, but there should have been a recent or past response to Ilumya was moved to a Note within the criteria.	04/22/2020

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, PJIA, PsO, PsA, RA, SJIA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: PJIA, PSA, RA
		IV formulation: PJIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Ilaris (canakinumab SC injection**)**	Inhibition of IL-1β	SJIA
Kineret® (anakinra SC injection)	Inhibition of IL-1	RA, SJIA^
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; PJIA – Polyarticular juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; SJIA – Systemic juvenile idiopathic arthritis; UC – Ulcerative colitis; ^ Off-label use of SJIA supported in guidelines.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Infliximab Products Prior Authorization Policy

- Avsola™ (infliximab-axxq intravenous infusion – Amgen)
- Inflectra™ (infliximab-dyyb intravenous infusion – Hospira/Pfizer)
- Remicade® (infliximab intravenous infusion – Janssen Biotech, Inc./Johnson & Johnson)
- Renflexis® (infliximab-abda intravenous infusion – Samsung Bioepis/Merck)

REVIEW DATE: 09/23/2020

OVERVIEW

Infliximab products are tumor necrosis factor inhibitors (TNFis) approved for the following indications:[1-3]

- **Ankylosing spondylitis**, for reducing signs and symptoms of active disease.
- **Crohn's disease**, for the following uses:
  - Reducing the signs and symptoms and inducing and maintaining clinical remission in patients ≥ 6 years of age with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy; AND
  - Reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adults with fistulizing Crohn's disease.
- **Plaque psoriasis**, for treatment of adults with chronic severe (i.e., extensive and/or disabling) disease who are candidates for systemic therapy and when other systemic therapies are less appropriate.
- **Psoriatic arthritis**, for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage and improving physical function.
- **Rheumatoid arthritis**, in combination with methotrexate for reducing signs and symptoms, inhibiting the progression of structural damage and improving physical function in patients with moderately to severely active disease.
- **Ulcerative colitis**, for the following uses:
  - Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adults with moderately to severely active disease who have had an inadequate response to conventional therapy; AND
  - Reducing signs and symptoms and inducing and maintaining clinical remission in patients ≥ 6 years of age with moderately to severely active disease who have had an inadequate response to conventional therapy.

Avsola, Inflectra and Renflexis were approved as biosimilar to Remicade, indicating no clinically meaningful differences in safety and effectiveness and the same mechanism of action, route of administration, dosage form, and strength as Remicade.[2-3] However, minor differences in clinically inactive components are allowed. At this time, only biosimilarity has been demonstrated (not interchangeability).

Guidelines

TNFis feature prominently in guidelines for treatment of many inflammatory conditions.

- **Spondyloarthritis:** Guidelines for ankylosing spondylitis and non-radiographic axial spondyloarthritis are published by the American College of Rheumatology (ACR)/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (2019).[4] Following primary nonresponse to a TNFi, an interleukin (IL)-17 blocker is recommended; however, if the patient is a secondary nonresponder, a second TNFi is recommended over switching out of the class. In patients with a contraindication to a TNFi, use of an IL-17 blocker is recommended over traditional oral agents such as methotrexate or sulfasalazine.
- **Crohn's Disease:** The American College of Gastroenterology (ACG) has guidelines for Crohn's disease (2018).[5] TNFis are listed as an option for disease that is resistant to corticosteroids, severely active disease, perianal fistulizing disease, and maintenance of remission. In post-operative Crohn's disease, a TNFi should be started within 4 weeks of surgery to prevent recurrence.
- **Plaque Psoriasis:** Guidelines from the American Academy of Dermatologists (AAD) and National Psoriasis Foundation (NPF) [2019] recommend infliximab as a monotherapy treatment option for adults with moderate to severe disease.[6]
- **Psoriatic Arthritis:** Guidelines from ACR (2019) recommend TNFis over other biologics for use in treatment-naïve patients with psoriatic arthritis, and in those who were previously treated with an oral therapy.[7]
- **Rheumatoid Arthritis:** Guidelines from the American College of Rheumatology (ACR) [2015] have TNF inhibitors and non-TNF biologics, administered with or without methotrexate, equally positioned as a recommended therapy following a trial of a conventional synthetic disease-modifying antirheumatic drug (DMARD) [e.g., methotrexate, leflunomide, hydroxychloroquine, sulfasalazine].[8]
- **Ulcerative Colitis:** Updated ACG guidelines for ulcerative colitis (2019) note that the following agents can be used for induction of remission in moderately to severely active disease: Uceris tablets; Oral or intravenous systemic corticosteroids Entyvio, Xeljanz, or TNFis.[9] In addition to the approved indication,

clinical guidelines for the management of pouchitis, published in 2009 indicate that first-line therapy for pouchitis is antibiotic therapy (e.g. metronidazole, ciprofloxacin).[11] Other treatment options include maintenance probiotics, oral or topical budesonide, anti-inflammatory drugs (e.g., mesalamine), or immunosuppressive drugs (e.g., infliximab). Guidelines from the American Gastroenterological Association (2020) recommend infliximab for moderate to severe ulcerative colitis.[11]

Other Uses with Supportive Evidence

There are guidelines and/or published data supporting the use of infliximab products in the following conditions:

- **Behcet's Disease:** The European League Against Rheumatism (EULAR) recommendations (2018) include TNFis for initial or recurrent sight-threatening uveitis.[12] For patients refractory to first-line treatments (e.g., corticosteroids), TNFis are among the treatment options for mucocutaneous manifestations, venous thrombosis, severe or refractory gastrointestinal disease, and recurrent/chronic joint involvement. Recommendations for the use of TNFis in ocular inflammatory disorders from the American Academy of Ophthalmology (AAO) [2014] notes that TNFis may be used first-line in patients with ophthalmic manifestations of Behcet's disease and for acute exacerbations of pre-existing Behcet's disease.[13]
- **Graft-Versus-Host Disease:** Guidelines from the National Comprehensive Cancer network (NCCN) [version 2.2020 – March 23, 2020] list infliximab among the agents used for steroid-refractory disease.[19]
- **Hidradenitis Suppurativa:** In a Phase II double-blind, placebo-controlled crossover trial, adult patients with moderate to severe hidradenitis suppurativa were randomized to placebo (n = 23) or infliximab 5 mg/kg (n = 15) at Weeks 0, 2, and 6.[25] After Week 8, patients were unblinded, and placebo patients were offered induction with placebo. Maintenance was continued through 22 weeks of treatment. Following Week 8, more patients in the infliximab-treatment group experienced a 50% or greater decrease in the Hidradenitis Suppurativa Severity Index (HSSI) score (approximately 26% and 5% of patients receiving infliximab and placebo, respectively [data presented graphically]; P = 0.092). In post-hoc analysis, significantly more patients treated with infliximab responded with a 25% to < 50% response (60% and 5.6% for infliximab and placebo, respectively; P < 0.001). Improvement was noted through Week 30. In case series, infliximab has been effective in treating hidradenitis suppurativa that was refractory to other therapies.[26-28]
- **Indeterminate Colitis:** Infliximab has been effective in some patients with refractory indeterminate colitis (retrospective reviews).[29,30] When patients who are refractory to standard therapy can be definitively classified as having ulcerative colitis, colectomy is considered an effective long-term surgical treatment. Patient's with Crohn's disease, however, have a high risk of complications after ileal pouch-anal anastomosis and are treated more aggressively with medical interventions since surgical options cannot offer the same likelihood of success as in ulcerative colitis.
- **Ocular Inflammatory Disorders:** Recommendations for the use of TNFis in ocular inflammatory disorders from the AAO (2014) note that infliximab may be used as second-line corticosteroid-sparing therapy for chronic and severe scleritis.[13] Infliximab may be used in patients with uveitis due to various causes (e.g., spondyloarthropathy-associated or human leukocyte antigen [HLA]-B27-associated uveitis, juvenile idiopathic arthritis-associated uveitis, and other posterior uveitides and panuveitis syndromes).[13] Infliximab should be considered second-line in vision-threatening JIA-associated uveitis when methotrexate has failed or is not tolerated (strong recommendation) and vision-threatening chronic uveitis from seronegative spondyloarthropathy (strong recommendation). Infliximab may also be considered in other patients who have vision-threatening or corticosteroid-dependent disease who have failed first-line therapies. The recommendations point out that studies evaluating infliximab in uveitis included patients with birdshot chorioretinitis (BSCR), a bilateral posterior uveitis generally treated with systemic immunomodulation; these patients showed a good response to infliximab.
- **Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitors:** NCCN has guidelines (version 1.2020 – December 16, 2020) for Management of Immunotherapy-Related Toxicities.[14] Infliximab is recommended to manage inflammatory arthritis, vision changes, and diarrhea/colitis. Some severe toxicities (e.g., pneumonitis, cardiac toxicity, renal failure) may also be treated with infliximab but are more likely to be administered in the hospital setting.
- **Juvenile Idiopathic Arthritis (JIA):** The ACR/Arthritis Foundation Guideline for the treatment of JIA (2019) provides updated recommendations for juvenile non-systemic polyarthritis, sacroiliitis, and enthesitis.[15] Infliximab is among the TNFis recommended as subsequent therapy following treatment with a conventional synthetic DMARD such as methotrexate. TNF antagonists such as infliximab may also be used as second- or third-line treatment for systemic JIA.[16]

- **Pyoderma Gangrenosum:** Although guidelines are not current, multiple topical and systemic therapies have been used for pyoderma gangrenosum. Oral prednisone is the most common initial immunosuppressant medication.[17] Other systemic therapies include cyclosporine, methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, and TNFis (i.e., infliximab, etanercept, and adalimumab products). In case reports, TNFis have been effective.
- **Still's Disease:** Still's disease presents in adults with features similar to those of systemic onset JIA.[31-32] In case series, infliximab has been effective in patients with Still's disease that was refractory to therapy with corticosteroids, methotrexate, azathioprine, and cyclophosphamide.[33]
- **Sarcoidosis:** Recommendations for best practice in the management of pulmonary and systemic sarcoidosis recommend glucocorticoids as first-line therapy.[18] Patients who cannot be weaned to a prednisone-equivalent dose of < 10 mg/day are appropriate candidates for steroid-sparing treatment with cytotoxic agents (e.g., methotrexate, azathioprine, leflunomide). If these agents fail or cause toxicity, adalimumab, infliximab, cyclophosphamide, or mycophenolate mofetil are proposed.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of infliximab products. Because of the specialized skills required for evaluation and diagnosis of patients treated with infliximab as well as the monitoring required for adverse events and long-term efficacy, initial approval requires infliximab to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration listed below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of infliximab products is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Ankylosing Spondylitis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if prescribed by or in consultation with a rheumatologist.
   - **B)** Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response as determined by the prescriber.
     Note: Examples of a response to therapy include decreased pain or stiffness, improved function or activities of daily living. Patient may not have a full response, but there should have been a recent or past response to an infliximab product.

2. **Crohn's Disease.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient is ≥ 6 years of age; AND
     - **ii.** Patient meets ONE of the following conditions (a, b, c, or d):
       - **a)** Patient has tried or is currently taking corticosteroids, or corticosteroids are contraindicated in this patient; OR
         Note: Examples of corticosteroids are prednisone and methylprednisolone.
       - **b)** Patient has tried one other conventional systemic therapy for Crohn's disease; OR
         Note: Examples of conventional systemic therapies for Crohn's disease include azathioprine, 6-mercaptopurine, or methotrexate. A previous trial of a biologic also counts as a trial of one other agent for Crohn's disease. Refer to Appendix for examples of biologics used for Crohn's disease.
       - **c)** Patient has enterocutaneous (perianal or abdominal) or rectovaginal fistulas; OR
       - **d)** Patient had ileocolonic resection (to reduce the chance of Crohn's disease recurrence); AND
     - **iii.** The medication is prescribed by or in consultation with a gastroenterologist.
   - **B)** Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response, as determined by the prescriber.

Note: Patient may not have a full response, but there should have been a recent or past response to an infliximab product.

3. Plaque Psoriasis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following criteria (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets ONE of the following conditions (a or b):

a) Patient has tried at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR

Note: Examples include methotrexate, cyclosporine, acitretin (Soriatane®, generics), or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient already had a 3-month trial or previous intolerance to at least one biologic. Refer to Appendix for examples of biologics used for psoriasis. These patients who have already tried a biologic for psoriasis are not required to "step back" and try a traditional systemic agent for psoriasis.

b) Patient has a contraindication to methotrexate, as determined by the prescriber; AND

iii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response, as determined by the prescriber.

Note: Patient may not have a full response, but there should have been a recent or past response to an infliximab product.

4. Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response as determined by the prescriber.

Note: Examples of a response include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improvements in acute phase reactants (for example, C-reactive protein). Patient may not have a full response, but there should have been a recent or past response to an infliximab product.

5. Rheumatoid Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following criteria (i and ii):

i. Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND

Note: Examples include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient already had a 3-month trial of at least one biologic. Refer to Appendix for examples of biologics used for rheumatoid arthritis. These patients who have already tried a biologic are not required to "step back" and try a conventional synthetic DMARD.

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response as determined by the prescriber.

Note: Examples of a response include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids. Patient may not have a full response, but there should have been a recent or past response to an infliximab product.

6. Ulcerative Colitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following criteria (i, ii, and iii):

i. Patient is ≥ 6 years of age; AND

ii. Patient meets ONE of the following conditions (a or b):

a) Patient had a trial of one systemic agent or was intolerant to one of these agents for ulcerative colitis; OR

Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone, methylprednisolone. A previous trial of a biologic also counts as a trial of one systemic agent for ulcerative colitis. Refer to Appendix for examples of biologics used for ulcerative colitis.

b) Patient meets BOTH of the following [(1) and (2)]:

(1) Patient has pouchitis; AND

(2) Patient has tried therapy with an antibiotic, probiotic, corticosteroid enema, or Rowasa® (mesalamine) enema; AND

Note: Examples of antibiotics include metronidazole and ciprofloxacin. Examples of corticosteroid enemas include hydrocortisone enema (Cortenema, generics).

iii. The medication is prescribed by or in consultation with a gastroenterologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response as determined by the prescriber.

Note: Examples of a response include decreased stool frequency or rectal bleeding. The patient may not have a full response, but there should have been a recent or past response to an infliximab product.

Other Uses with Supportive Evidence

7. Behcet's Disease. Approve for the duration noted if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following conditions (i and ii):

i. Patient meets ONE of the following (a or b):

a) Patient has tried at least ONE conventional therapy; OR

Note: Examples include systemic corticosteroids (e.g., methylprednisolone), immunosuppressants (azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, tacrolimus, Leukeran® [chlorambucil], cyclophosphamide, interferon alfa). An exception to the requirement for a trial of one conventional therapy can be made if the patient has already had a trial of at least one tumor necrosis factor inhibitor (e.g., an adalimumab product, an etanercept product). These patients who have already tried a biologic for Behcet's disease are not required to "step back" and try a conventional therapy.

b) Patient has ophthalmic manifestations of Behcet's disease; AND

ii. The medication is prescribed by or in consultation with a rheumatologist, dermatologist, ophthalmologist, gastroenterologist, or neurologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response, as determined by the prescriber.

Note: Patient may not have a full response by Month 2 or 3, but there should be some response.

8. Graft-Versus-Host Disease. Approve for the duration noted if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve for 1 month if the patient meets BOTH of the following (i and ii):

i. Patient has tried at least one conventional systemic treatment for graft-versus-host disease; AND

Note: Examples of conventional treatments include corticosteroids (e.g., methylprednisolone), antithymocyte globulin, cyclosporine, tacrolimus, and mycophenolate mofetil.

ii. The medication is prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center; OR

B) Patient is Currently Receiving an Infliximab Product. Approve for 3 months if the patient had a response, as determined by the prescriber.

9. Hidradenitis Suppurativa. Approve for the duration noted if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (i and ii):

i. Patient has tried one other therapy; AND

Note: Examples include intralesional or oral corticosteroids (e.g., triamcinolone, prednisone), systemic antibiotics (e.g., clindamycin, dicloxacillin, erythromycin), and isotretinoin.

ii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response, as determined by the prescriber.

10. Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy. Approve for the duration noted if the patient meets ONE of the following (A or B):

C) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, iii, and iv):

i. Patient developed an immunotherapy-related toxicity involving the gastrointestinal system, inflammatory arthritis, or ocular toxicity; AND
Note: An example of a gastrointestinal system toxicity is colitis. Examples of ocular toxicities include uveitis/iritis, episcleritis, and blepharitis.

ii. Patient developed this immune-related toxicity while receiving a checkpoint inhibitor; AND
Note: Examples of checkpoint inhibitors include Keytruda (pembrolizumab intravenous [IV] infusion), Opdivo (nivolumab IV infusion), Yervoy (ipilimumab IV infusion), Tecentriq (atezolizumab IV infusion), Bavencio (avelumab IV infusion), or Imfinzi (durvalumab IV infusion).

iii. Patient has tried one systemic corticosteroid; AND
Note: Examples include methylprednisone and prednisone.

iv. The medication is prescribed by or in consultation with an oncologist, gastroenterologist, rheumatologist, or ophthalmologist; OR

D) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient has responded and needs continued treatment, as determined by the prescriber.

11. Indeterminate Colitis (defined as colitis that cannot be classified with certainty as either ulcerative colitis or Crohn's disease). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets ALL of the following (i, ii, iii, iv, and v):

i. Patient is ≥ 6 years of age; AND

ii. Patient has tried one systemic corticosteroid; AND
Note: Examples include prednisone and methylprednisolone.

iii. Patient has tried mesalamine; AND

iv. Patient has tried either azathioprine or 6-mercaptopurine; AND

v. The medication is prescribed by or in consultation with a gastroenterologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response, as determined by the prescriber.

12. Juvenile Idiopathic Arthritis (JIA) [or Juvenile Rheumatoid Arthritis] (regardless of type of onset) [Note: This includes patients with juvenile spondyloarthropathy/active sacroiliac arthritis]. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following criteria (i and ii):

i. Patient meets ONE of the following conditions (a or b):

a) Patient has tried one other medication for this condition; OR
Note: Examples of other medications for JIA include methotrexate, sulfasalazine, or leflunomide, a nonsteroidal anti-inflammatory drug (NSAID) [e.g., ibuprofen, naproxen]. A previous trial of a biologic also counts as a trial of one medication. Refer to Appendix for examples of biologics used for JIA.

b) Patient has aggressive disease, as determined by the prescriber; AND

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response as determined by the prescriber.
Note: Examples of a response include improvement in limitation of motion, less joint pain or tenderness, decreased duration of morning stiffness or fatigue, improved function or activities of daily living, reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to an infliximab product.

13. Pyoderma Gangrenosum. Approve for the duration noted if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets BOTH of the following conditions (i and ii):
- **i.** Patient meets ONE of the following conditions (a or b):
  - **A)** Patient has tried one systemic corticosteroid; OR
    Note: An example is prednisone.
  - **B)** Patient has tried one other immunosuppressant for at least 2 months or was intolerant to one of these medications; AND
    Note: Examples include mycophenolate mofetil and cyclosporine.
- **ii.** The medication is prescribed by or in consultation with a dermatologist; OR

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response, as determined by the prescriber.
Note: Patient may not have a full response by Month 4 or 5 (after 4 doses), but there should be some response.

14. Sarcoidosis. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following conditions (i, ii, and iii):
- **i.** Patient has tried at least one corticosteroid; AND
  Note: An example is prednisone.
- **ii.** Patient has tried at least one immunosuppressive medication; AND
  Note: Examples include methotrexate, azathioprine, cyclosporine, Leukeran, Thalomid® (thalidomide capsules), or chloroquine.
- **iii.** The medication is prescribed by or in consultation with a pulmonologist, ophthalmologist, or dermatologist; OR

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response, as determined by the prescriber.
Note: The patient may not have a full response by Month 3, but there should be some response.

15. Scleritis or Sterile Corneal Ulceration. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following conditions (i and ii):
- **i.** Patient has tried one other therapy for this condition; AND
  Note: Examples include oral non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin; oral, topical (ophthalmic) or intravenous corticosteroids (such as prednisone, prednisolone, methylprednisolone); methotrexate; cyclosporine; or other immunosuppressants.
- **ii.** The medication is prescribed by or in consultation with an ophthalmologist; OR

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response as determined by the prescriber.
Note: Examples of a response to therapy include decreased inflammation, reduced use of steroids or immunomodulators, decreased eye pain, redness, and/or photophobia. The patient may not have a full response by Month 2 or 3, but there should be some response.

16. Still's Disease. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following conditions (i, ii, and iii):
- **i.** Patient has tried one corticosteroid; AND
  Note: An example is prednisone.
- **ii.** Patient has tried one conventional synthetic disease-modifying antirheumatic drug (DMARD) given for at least 2 months or was intolerant; AND
  Note: An example is methotrexate.
- **iii.** The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response, as determined by the prescriber.

Note: Patient may not have a full response by Month 2 or 3, but there should be some response.

17. **Spondyloarthritis, Other Subtypes** (Note: Examples of other subtypes include undifferentiated arthritis, non-radiographic axial spondylitis, Reactive Arthritis [Reiter's disease]. For ankylosing spondylitis or psoriatic arthritis, refer to the respective criteria under FDA-approved indications). Approve for the duration noted if ONE of the following conditions are met (A or B):
    E) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following conditions (i and ii):
        i. Patient meets ONE of the following (a or b):
            a) Patient has arthritis primarily in the knees, ankles, elbows, wrists, hands, and/or feet AND has tried at least ONE conventional synthetic disease-modifying antirheumatic drug (DMARD); OR
            Note: Examples include methotrexate, leflunomide, and sulfasalazine.
            b) Patient has axial spondyloarthritis with objective signs of inflammation, defined as at least one of the following [(1) or (2)]:
                a) C-reactive protein elevated beyond the upper limit of normal for the reporting laboratory; OR
                b) Sacroiliitis reported on magnetic resonance imaging; AND
        ii. The medication is prescribed by or in consultation with a rheumatologist; OR
    F) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response as determined by the prescriber.
    Note: Examples of a response include decreased pain or stiffness, improved function or activities of daily living. The patient may not have a full response, but there should have been a recent or past response to an infliximab product.

18. **Uveitis (including other posterior uveitides and panuveitis syndromes).** Approve for the duration noted if the patient meets ONE of the following criteria (A or B):
    A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following conditions (i and ii):
        i. Patient has tried one of the following therapies: periocular, intraocular, or systemic corticosteroids, or immunosuppressives; AND
        Note: Examples of corticosteroids include prednisolone, triamcinolone, betamethasone, methylprednisolone, prednisone. Examples of immunosuppressives include methotrexate, mycophenolate mofetil, and cyclosporine. An exception to the requirement for a trial of one of these therapies can be made if the patient has already had a trial of an etanercept product or an adalimumab product for uveitis. These patients who have already tried a biologic for uveitis are not required to try another medication.
        ii. The medication is prescribed by or in consultation with an ophthalmologist.
    B) Patient is Currently Receiving an Infliximab Product. Approve for 1 year if the patient had a response as determined by the prescriber.
    Note: Examples of a response include decreased inflammation, reduced use of steroids or immunomodulators, and improvement in visual acuity. The patient may not have a full response by Month 2 or 3, but there should be some response.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of infliximab products is not recommended in the following situations:

1. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Data are lacking evaluating concomitant use of an infliximab product in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see APPENDIX for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMARDs has a potential for a higher

rate of AEs and lack controlled trial data in support of additive efficacy. Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with an infliximab product.

2. **Inflammatory Myopathies (Polymyositis, Dermatomyositis, Inclusion Body Myositis).** Exceptions are not recommended. In an open-label pilot study in 13 patients, four infliximab 5 mg/kg infusions given over 14 weeks were not effective in refractory inflammatory myopathies.[36] Infliximab could worsen muscle inflammation in these patients.

3. **Large Vessel Vasculitis (e.g., Giant Cell Arteritis, Takayasu's Arteritis).** Guidelines from EULAR for the management of large vessel vasculitis (e.g., giant cell arteritis, Takayasu's arteritis) do not mention the use of TNF blockers.[37] Additionally, a meta-analysis of RCTs did not find evidence supporting remission or reduction of corticosteroid dose with the use of TNF blockers in large vessel vasculitis.[38] In a controlled trial, 44 patients with newly diagnosed giant cell arteritis that was in glucocorticoid-induced remission were randomized to infliximab 5 mg/kg plus glucocorticoid (n = 28) or placebo plus glucocorticoid (n = 16).[39] Infliximab did not increase the percentage of patients without relapse at Week 22 nor did it increase the percentage of patients whose glucocorticoid dose was decreased to 10 mg/day without relapse. Use of TNF blockers such as infliximab for Takayasu's arteritis is limited to case series where TNF blockers are often used third line, after treatment with corticosteroids and other immunosuppressants (e.g., azathioprine, MTX, cyclophosphamide).[40-44] Infliximab has been effective in a very limited number of patients with vasculitis (e.g., RA, cryoglobulinemia, polyangiitis, polymyalgia rheumatica, Takayasu's arteritis) who were refractory to standard therapy.[40-41,45-49] However, in a randomized study in 51 patients with newly diagnosed polymyalgia rheumatica, adding infliximab 3 mg/kg to prednisone was of no benefit and may have been harmful.[50-51]

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Immunotherapy-Related Toxicity Related to Checkpoint Inhibitor Therapy:** New indication added to align with guidelines for patients who develop gastrointestinal, joint, or ophthalmic toxicity while on a checkpoint inhibitor. Approval is for 3 months, if the patient has tried a corticosteroid, and if prescribed by or in consultation with a gastroenterologist, ophthalmologist, rheumatologist, or oncologist. Reauthorization is for 1 year, if the patient responded and needs continued treatment, according to the prescriber. **Patients Established on Infliximab:** Remove this criterion for patients currently established on infliximab for ≥ 90 days. Patients currently taking infliximab are now addressed in the criteria section for each specific indication. • To align with the infliximab Prior Authorization Policy, remove requirement that the patient be receiving infliximab for ≥ 90 days for the following indications: rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, plaque psoriasis, psoriatic arthritis, ulcerative colitis, and juvenile idiopathic arthritis. • Add a requirement that the patient must have responded to initial therapy for the following indications: Behcet's disease, graft versus host disease, hidradenitis suppurativa, indeterminate colitis, pyoderma gangrenosum, sarcoidosis, slceritis or sterile corneal ulcerations, Still's disease, spondyloarthritis, and uveitis. **Previous Therapies:** For these indications, add the following agents to the list of therapies the patient may have tried prior to infliximab: • CD: Stelara Intravenous/Subcutaneous • PsO: Cimzia, Illumya, Siliq, Tremfya • UC: Entyvio • JIA: Actemra SC **Behcet's disease:** Modify criteria to change previous therapy from biologic to more specifically say tumor necrosis factor inhibitor. **Other:** Throughout the policy, references to Humira and Enbrel were reworded as adalimumab and etanercept products, respectively, with the innovator names listed as examples of these products.	08/01/2018
Selected Revision	**Ulcerative colitis:** For the requirement that another agent be tried prior to Entyvio, remove the requirement that the trial is a duration of at least 2 months (not supported in updated guidelines).	03/27/2019
Selected Revision	**Spondyloarthritis (SpA), Other Subtypes:** This off-label approval condition was reworded (previously listed as Spondyloarthritis, Subtypes Other than Ankylosing Spondylitis or Psoriatic Arthritis). There is a note which directs to criteria for FDA-approved subtypes of SpA (AS, PsA). For patients with primarily axial disease, a criterion was added to require objective signs of inflammation, defined as C-reactive protein (CRP) elevated beyond the upper limit of normal for the reporting laboratory or sacroiliitis reported on magnetic resonance imaging. For patients currently receiving therapy, examples of a response to therapy were added; the requirement that patients be on an infliximab product for ≥ 90 days was removed.	04/24/2019
Annual Revision	**Crohn's Disease:** Move requirement that the patient be 6 years of age or older into the criteria section for initial therapy. Previously, age was listed as part of the diagnosis (i.e., previously listed as Crohn's disease in a patient ≥ 6 years of age) and applied to initial and continuation of therapy. **Plaque Psoriasis:** For the exception applying to patients with a contraindication to methotrexate, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). Skyrizi was added to the list of biologics that the patient may have tried prior to infliximab. **Rheumatoid Arthritis:** Truxima was added to as an example of a rituximab product that the patient may have tried prior to infliximab. **Ulcerative Colitis:** Move requirement that the patient be 6 years of age or older into the criteria section for initial therapy. Previously, age was listed as part of the diagnosis (i.e., previously listed as Ulcerative Colitis in a patient ≥ 6 years of age) and applied to initial and continuation of therapy. **Behcet's Disease:** For patients currently receiving therapy, the requirement that patients be on an infliximab product for ≥ 90 days was removed. **Graft versus Host Disease:** For patients currently receiving therapy, the requirement that patients be on an infliximab product for ≥ 90 days was removed.	08/28/2019

	Hidradentitis Suppurativa: For patients currently receiving therapy, the requirement that patients be on an infliximab product for ≥ 90 days was removed, the requirement that patients be on an infliximab product for ≥ 90 days was removed. **Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitor Therapy:** When a response to therapy is required for patients continuing infliximab, wording was changed to be according to the prescriber (previously worded as prescribing physician). **Indeterminate Colitis:** Move requirement that the patient be 6 years of age or older into the criteria section for initial therapy. Previously, age was listed as part of the diagnosis (i.e., previously listed as Indeterminate Colitis in a patient ≥ 6 years of age) and applied to initial and continuation of therapy. For patients currently receiving therapy, the requirement that patients be on an infliximab product for ≥ 90 days was removed. **Juvenile Idiopathic Arthritis:** For the exception applying to patients with aggressive disease, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). **Pyoderma Gangrenosum:** For patients currently receiving therapy, the requirement that patients be on an infliximab product for ≥ 90 days was removed. **Sarcoidosis:** For patients currently receiving therapy, the requirement that patients be on an infliximab product for ≥ 90 days was removed. When a response to therapy is required for patients continuing infliximab, wording was changed to be according to the prescriber (previously worded as prescribing physician). **Scleritis/Sterile Corneal Ulceration:** For patients currently receiving therapy, the requirement that patients be on an infliximab product for ≥ 90 days was removed. When a response to therapy is required for patients continuing infliximab, wording was changed to be according to the prescriber (previously worded as prescribing physician). **Still's Disease:** For patients currently receiving therapy, the requirement that patients be on an infliximab product for ≥ 90 days was removed. **Uveitis:** For patients currently receiving therapy, the requirement that patients be on an infliximab product for ≥ 90 days was removed. When a response to therapy is required for patients continuing infliximab, wording was changed to be according to the prescriber (previously worded as prescribing physician).	
DEU Revision	**Overview:** Update to include new approval indications for biosimilars. No changes to the criteria.	11/25/2019
Selected Revision	Avsola (infliximab-axxq for injection, for intravenous use) [biosimilar to Remicade] was added to the policy. Criteria are the same as for the other infliximab products. Throughout the policy, examples of infliximab products were replaced with a general reference to infliximab products.	06/03/2020
Annual Revision	**Crohn's Disease:** Examples of biologics were moved to be included in the Appendix (previously listed in a Note in the criteria section). For the criterion applying to previous therapy, wording was changed to specify this must have been a conventional systemic therapy (criteria previously required a trial of one other agent, with conventional systemic agents listed among the examples). **Plaque Psoriasis:** Examples of biologics were moved to be included in the Appendix (previously listed in a Note in the criteria section). **Rheumatoid Arthritis:** Examples of biologics were moved to be included in the Appendix (previously listed in a Note in the criteria section). **Ulcerative Colitis:** Examples of biologics were moved to be included in the Appendix (previously listed in a Note in the criteria section). **Graft Versus Host Disease (GVHD):** To align with updated NCCN guidelines and other policies, criteria were changed to require at least one conventional systemic treatment prior to an infliximab product. Previously, criteria required that the patient had tried at least one other immunosuprressant or be concurrently receiving an immunosuppressant in combination with an infliximab product. **Juvenile Idiopathic Arthritis:** Examples of biologics were moved to be included in the Appendix (previously listed in a Note in the criteria section).	09/23/2020

APPENDIX

Biologic	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzaa SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic Disease-Modifying Antirheumatic Drugs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous; PJIA – Polyarticular juvenile idiopathic arthritis; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; JAK – Janus kinase.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Kevzara Prior Authorization Policy

- Kevzara™ (sarilumab for subcutaneous injection – Regeneron)

REVIEW DATE: 07/01/2020

OVERVIEW

Kevzara, an interleukin-6 (IL-6) receptor inhibitor, is indicated for the treatment of rheumatoid arthritis in adults with moderate to severe active disease who have had an inadequate response or intolerance to one or more disease-modifying anti-rheumatic drugs (DMARDs).[1] Kevzara + conventional synthetic (cs)DMARD has demonstrated superior efficacy over placebo + csDMARD as assessed by American College of Rheumatology (ACR) responses, physical function, and radiographic progression.

Guidelines

Guidelines from the American College of Rheumatology (ACR) [2015], last updated prior to the approval of Kevzara, have TNF inhibitors and non-TNF biologics, administered with or without MTX, equally positioned as a recommended therapy following a trial of a conventional synthetic DMARD (e.g., MTX, leflunomide, hydroxychloroquine, sulfasalazine).[2] Guidelines for treatment of inflammatory conditions recommend assessment of response to initial therapy, most often within 3 months of initiating or changing therapy.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Kevzara. Because of the specialized skills required for evaluation and diagnosis of patients treated with Kevzara as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Kevzara to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the approval duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

All reviews for use of Kevzara for COVID-19 and/or cytokine release syndrome associated with COVID-19 will be forwarded to the Medical Director.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kevzara is recommended in those who meet one of the following criteria:

FDA-Approved Indications

13. Rheumatoid Arthritis. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following criteria (i and ii):

i. Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND

Note: Examples of conventional synthetic DMARDs include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already had a 3-month trial of at least one biologic. Refer to Appendix for examples of biologics used for rheumatoid arthritis. These patients who have already tried a biologic are not required to "step back" and try a conventional synthetic DMARD).

ii. Kevzara is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Kevzara. Approve for 3 years if the patient has had a response, as determined by the prescriber.

Note: Examples of a response to therapy include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Kevzara.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kevzara is not recommended in the following situations:

4. Ankylosing Spondylitis. In a Phase II study, Kevzara did not demonstrate efficacy in patients with AS.[3]

5. Concurrent use with a Biologic or with a Targeted Synthetic DMARD. Kevzara should not be administered in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see Appendix for examples). Combination therapy is generally not recommended due to a potential for a higher rate of adverse effects with combinations and lack of evidence for additive efficacy. Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Kevzara.

3. COVID-19 (Coronavirus Disease 2019). Forward all requests to the Medical Director.[4-6]
Note: This includes requests for cytokine release syndrome associated with COVID-19.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	Throughout the policy, references to Humira, Enbrel, and Rituxan were reworded as adalimumab, etanercept, and rituximab products, respectively, with the innovator names listed as examples of these products. Erelzi was added as an example of an etanercept product.	05/30/2018
Annual revision	**Rheumatoid Arthritis:** Truxima was added to the list of therapies the patient may have tried prior to Kevzara.	06/18/2019
Selected revision	**COVID-19:** This indication (including use in cytokine release syndrome associated with COVID-19) was added to the policy as a Condition Not Recommended for Coverage. All reviews are directed to the Medical Director.	03/25/2020
Annual revision	**Rheumatoid Arthritis:** Examples of conventional synthetic disease-modifying antirheumatic drugs were moved to a Note (previously listed as examples within the criteria). Examples of biologics for Rheumatoid Arthritis were moved to be included in the Appendix (previously listed in a Note in the criteria section).	07/01/2020

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, PJIA, PsO, PsA, RA, SJIA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: PJIA, PSA, RA
		IV formulation: PJIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Ilaris (canakinumab SC injection**)**	Inhibition of IL-1β	SJIA
Kineret® (anakinra SC injection)	Inhibition of IL-1	RA, SJIA^
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; PJIA – Polyarticular juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; SJIA – Systemic juvenile idiopathic arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; ^ Off-label use of SJIA supported in guidelines; DMARDs – Disease-modifying antirheumatic drugs.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Kineret Prior Authorization

- Kineret® (anakinra for subcutaneous injection – Biovitrim)

REVIEW DATE: 01/20/2021

OVERVIEW

Kineret, an interleukin-1 (IL-1) receptor antagonist, indicated for the following uses:[1]

- **Cryopyrin-associated periodic syndromes** (CAPS) for treatment of neonatal-onset multisystem inflammatory disease (NOMID).

- **Deficiency of interleukin-1 receptor antagonist** (DIRA).
- **Rheumatoid arthritis**, to reduce the signs and symptoms and slow the progression of structural damage in adult patients with moderately to severely active disease who have failed one or more disease-modifying antirheumatic drugs (DMARDs) given ± DMARDs other than tumor necrosis factor inhibitors (TNFis).

Guidelines

IL-1 blockers are used for treatment of multiple inflammatory conditions:

- **CAPS:** CAPS encompasses three rare genetic syndromes (familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and NOMID or chronic infantile neurological cutaneous and articular syndrome) that are thought to be one condition along a spectrum of disease severity.[2,3] In many cases, patients with CAPS reported an immediate clinical response to Kineret with rash, fever, and arthritis disappearing within a few days and not recurring during follow-up.[4] Dramatic and persistent normalization of inflammatory markers and hematologic tests have also been achieved.
- **DIRA:** Dysregulation of IL-1 signaling is prominent among autoinflammatory conditions such as DIRA. Thus, Kineret has been successfully used and is indicated to treat DIRA. The approval was based on a natural-history study in nine patients (aged 1 month to 9 years at baseline) with genetically confirmed DIRA.[1] Patients were treated with Kineret for up to 10 years. All nine patients achieved remission while on Kineret for DIRA. In some patients, skin and bone manifestations resolved within days and weeks, respectively.
- **Rheumatoid Arthritis:** Current recommendations for the treatment of rheumatoid arthritis from the American College of Rheumatology (ACR) [2015] do not make a recommendation for the use of Kineret.[5] The recommendations also note that Kineret is used infrequently for rheumatoid arthritis and that TNFis and other non-TNFi biologics (i.e., rituximab, Actemra (tocilizumab intravenous infusion, tocilizumab subcutaneous injection], and Orencia [abatacept intravenous infusion, abatacept subcutaneous injection]) are appropriate initial biologic therapy for most patients with rheumatoid arthritis.
- **Systemic Juvenile Idiopathic Arthritis (SJIA):** The 2013 update of the 2011 ACR recommendations for the treatment of SJIA advise Kineret as appropriate initial therapy in SJIA for patients with active systemic features and varying degrees of synovitis. Kineret is also considered an appropriate second- and third-line agent for all patients with SJIA (in patients with and without active systemic features). Macrophage activation syndrome is a severe and potentially lethal complication associated with SJIA.[7] Case-series have shown rapid remission of macrophage activation syndrome as well as treatment of the underlying condition with the use of Kineret.
- **Still's Disease:** Still's disease presents in adults with features similar to those of SJIA.[8] As in SJIA, Kineret has been effective in reducing fever, symptoms, and markers of inflammation in patients with adult-onset Still's disease who were refractory to conventional treatment with a corticosteroid, nonsteroidal anti-inflammatory drug (NSAID), and/or conventional synthetic DMARDs such as methotrexate.[9-14]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Kineret. Because of the specialized skills required for evaluation and diagnosis of patients treated with Kineret as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Kineret to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

All reviews for use of Kineret for COVID-19 and/or cytokine release syndrome associated with COVID-19 will be forwarded to the Medical Director.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kineret is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Cryopyrin-Associated Periodic Syndromes.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets BOTH of the following criteria (i and ii):
     - **i.** The medication is being used for treatment of neonatal onset multisystem inflammatory disease (NOMID), familial cold autoinflammatory syndrome (FCAS), Muckle-Wells Syndrome (MWS), and/or chronic infantile neurological cutaneous and articular (CINCA) syndrome; AND
     - **ii.** The medication is prescribed by or in consultation with a rheumatologist, geneticist, or a dermatologist.
   - **B)** Patient is Currently Receiving Kineret. Approve for 3 years if the patient has had a response, as determined by the prescriber.
     Note: Patient may not have a full response, but there should have been a recent or past response to Kineret.

2. **Deficiency of Interleukin-1 Receptor Antagonist**. Approve for the duration noted if the patient meets one of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (i and ii):
     - **i.** Genetic testing has confirmed a mutation in the *IL1RN* gene; AND
     - **ii.** The medication is prescribed by or in consultation with a rheumatologist, geneticist, dermatologist, or a physician specializing in the treatment of autoinflammatory disorders.
   - **B)** Patient is Currently Receiving Kineret. Approve for 3 years if the patient had a response, as determined by the prescriber.
     Note: Examples of a response include normalized acute phase reactants; resolution of fever, skin rash, and bone pain; and reduced dosage of corticosteroids.

3. **Rheumatoid Arthritis**. Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets BOTH of the following criteria (i and ii):
     - **i.** Patient has had a 3-month trial of a biologic OR targeted synthetic disease-modifying antirheumatic drug (DMARD) for this condition, unless intolerant; AND
       Note: Refer to Appendix for examples of biologics and targeted synthetic DMARDs used for rheumatoid arthritis. Conventional synthetic DMARDs such as methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine do not count.
     - **ii.** The medicaion is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Kineret. Approve for 3 years if the patient has had a response, as determined by the prescriber.

Note: Examples of response include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Kineret.

Other Uses with Supportive Evidence

4. Systemic Juvenile Idiopathic Arthritis (SJIA). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following criteria (i and ii):

i. Patient meets ONE of the following conditions (a, b, or c):

a) Patient has tried one other systemic agent for this condition; OR

Note: Examples of one other systemic agent include a corticosteroid (oral, intravenous); a conventional synthetic disease-modifying antirheumatic drug (DMARD; e.g., methotrexate, leflunomide, sulfasalazine); or a 1-month trial of a nonsteroidal anti-inflammatory drug (NSAID). A previous trial of a biologic (e.g, Actemra [tocilizumab intravenous injection, tocilizumab subcutaneous injection), a tumor necrosis factor inhibitor (e.g., an etanercept product [Enbrel, biosimilars], an adalimumab product [Humira, biosimilars], or an infliximab product [Remicade, biosimilars), or Ilaris (canakinumab subcutaneous injection) also counts towards a trial of one other systemic agent for SJIA.

b) Patient has at least moderate to severe active systemic features of this condition OR the patient has active systemic features with an active joint count of one joint or greater, according to the prescriber; OR

Note: Examples of moderate to severe active systemic features include fever, rash, lymphadenopathy, hepatomegaly, splenomegaly, and serositis.

c) Patient has active systemic features with concerns of progression to macrophage activation syndrome (MAS), as determined by the prescriber; AND

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Kineret. Approve for 3 years if the patient has responded, as determined by the prescriber.

Note: Examples of response include improvement in limitation of motion; less joint pain or tenderness; decreased duration of morning stiffness or fatigue; improved function or activities of daily living; reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Kineret.

5. Still's Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following criteria (i and ii):

i. Patient meets ONE of the following conditions (a, b, or c):

a) Patient meets ALL of the following criteria (1 and 2):

(1) Patient has tried one corticosteroid; AND

(2) Patient has had an inadequate response to one conventional synthetic disease-modifying antirheumatic drug (DMARD) such as methotrexate given for at least 2 months or was intolerant to a conventional synthetic DMARD; OR

Note: A previous trial of a biologic (e.g., Actemra [tocilizumab intravenous injection, tocilizumab subcutaneous injection], Arcalyst [rilonacept subcutaneous injection], Ilaris [canakinumab subcutaneous injection]) also counts towards a trial of one other systemic agent for Still's disease.

b) Patient has at least moderate to severe active systemic features of this condition, according to the prescriber; OR
Note: Examples of moderate to severe active systemic features include fever, rash, lymphadenopathy, hepatomegaly, splenomegaly, and serositis.

c) Patient has active systemic features with concerns of progression to macrophage activation syndrome, as determined by the prescriber; AND

ii. The medication is prescribed by or in consultation with a rheumatologist; OR

B) Patient is Currently Receiving Kineret. Approve for 1 year if the patient has responded, as determined by the prescriber.
Note: Examples of response include improvement in limitation of motion; less joint pain or tenderness; decreased duration of morning stiffness or fatigue; improved function or activities of daily living; reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Kineret.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kineret is not recommended in the following situations:

1. **Ankylosing Spondylitis.** Kineret has been beneficial in a few patients with ankylosing spondylitis, but results are not consistent.[15,16] In a small open-label study, patients with active ankylosing spondylitis who were refractory to NSAIDs (n = 20) received Kineret 100 mg daily.[16] The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score decreased over a 6-month period but was not significant (5.8 at baseline vs. 5.0 at Week 12, and 4.8 at Week 24). No significant change was found in Bath Ankylosing Spondylitis Functional Index (BASFI), patients' and physicians' global assessment or general pain during the study. After 12 weeks, both the assessment in ankylosing spondylitis (ASAS) 20 and 40 responses improved in 10.5% of patients (intent-to-treat analysis). After 24 weeks, ASAS 20 was attained in 26% of patients, ASAS 40 in 21% of patients, and ASAS 70 in 10.5% of patients. Guidelines for axial spondyloarthritis from the Assessment of SpondyloArthritis International Society (ASAS)/European Union Against Rheumatism (EULAR) [2016] do not mention Kineret as a treatment option.[17]

2. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Data are lacking evaluating concomitant use of Kineret in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (See Appendix for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMRADs has a potential for a higher rate of adverse effects and lack controlled trial data in support of additive efficacy.[18]
Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Kineret.

4. **COVID-19 (Coronavirus Disease 2019).** Forward all requests to the Medical Director.
Note: This includes requests for cytokine release syndrome associated with COVID-19.

3. **Lupus Arthritis.** The effectiveness and safety of Kineret were evaluated in an open 3-month pilot trial in patients (n = 4) with systemic lupus erythematosis (SLE) and severe, therapy-refractory non-erosive polyarthritis (three patients had deforming Jaccoud's arthropathy) and no other uncontrolled major organ involvement.[19] Patients were refractory to NSAIDs, antimalarials, corticosteroids, methotrexate,

cyclophosphamide, and azathioprine. SLE was controlled with stable doses of corticosteroids and/or antirheumatic or immunosuppressive agents; pain was managed with NSAIDs and/or other medications. Patients had improved clinically after 4 weeks on Kineret, but after 12 weeks the clinical activity parameters tended to increase again. The results from this study are preliminary and a larger controlled study is needed.

4. **Osteoarthritis.** In a Phase II study in patients with painful osteoarthritis of the knee, Kineret 150 mg administered by intraarticular injection was well tolerated.[20] The study was not designed to assess the analgesic efficacy of Kineret. Patients with osteoarthritis of the knee were enrolled in a multicenter, double-blind, placebo-controlled study and randomized to Kineret 50 mg, Kineret 150 mg, or placebo for intraarticular injection.[21] Although the injections were well tolerated, there were no significant differences in improvement in knee pain, stiffness, function or cartilage turnover between Kineret doses and placebo. Similar to other studies in this population, there was a significant placebo effect noted.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	Rheumatoid arthritis: Truxima was added as an example of a rituximab product. Oluminat was added as an example of a targeted synthetic disease-modifying antirheumatic drug that could have been taken prior to approval of Kineret.	03/27/2019
Annual revision	**Rheumatoid Arthritis:** Examples of biologics and targeted synthetic disease-modifying antirheumatic drugs were moved to a Note in the policy (previously listed as examples within the criteria). Examples of biologics for rheumatoid arthritis were moved to be included in the Appendix (previously listed in a Note in the criteria section). Examples of a response to therapy were moved to a Note in the policy (previously listed as examples within the criteria). **Cryopyrin-Associated Periodic Syndromes:** The explanation that the patient may not have a full response, but there should have been a recent or past response to Kineret was moved to a Note in the policy (previously stated within criteria). **Systemic Juvenile Idiopathic Arthritis (SJIA):** Examples of one other systemic agent tried for SJIA were moved to a Note in the policy (previously listed as examples within the criteria). Examples of moderate to severe active systemic features were moved to a Note in the policy (previously listed as examples within the criteria). For the exception applying to patients with at least moderate to severe active systemic features of this condition OR the patient has active systemic features with an active joint count of one joint or greater, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). For the exception applying to patients currently receiving Kineret who have responded, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). Examples of a response to therapy were moved to a Note in the policy (previously listed as examples within the criteria). **Still's Disease:** Criteria were changed to approve for 3 months for patients starting therapy (previously was 1 year). A note was added stating that patients who have already tried a biologic are not required to try one csDMARD for Still's disease prior to approval of Kineret. Exceptions were added for patients if, according to the prescriber, have moderate to severe active features OR active systemic features with concerns of progression to macrophage activation syndrome; these patients are not required to try any other therapies prior to Kineret for Still's disease. For patients currently receiving therapy, examples of a response to therapy were added; the requirement that patients be on Kineret for ≥ 90 days was removed. **COVID-19:** This indication (including use in cytokine release syndrome associated with COVID-19) was added to the policy as a Condition Not Recommended for Coverage. All reviews are directed to the Medical Director.	04/01/2020
Early Annual Revision	**Deficiency of Interleukin-1 Receptor Antagonist:** Criteira for this newly approved condition were added to the policy. For an initial 3-month approval, genetic testing must have confirmed a mutation in the *IL1RN* gene. Additionally, Kineret must be prescribed by or in consultation with a specialist. For a patient currently taking Kineret, a 3-year approval is authorized in the patient has responded to therapy. **Conditions Not Recommended for Coverage:** Under **Osteoarthritis** the qualifier "symptomatic" was removed from the indication for clarity. All requests for osteoarthritis remain denials.	01/20/2021

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		

Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of JAK pathways	RA
Xeljanz® (tofacitinib tablets)	Inhibition of JAK pathways	RA, PJIA, PsA, UC
Xeljanz® XR (tofacitinib extended-release tablets)	Inhibition of JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; ^ Off-label use of Kineret in JIA supported in guidelines; DMARDs – Disease-modifying antirheumatic drug.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Olumiant Prior Authorization Policy

- Olumiant (baricitinib tablets – Lilly)

REVIEW DATE: 07/01/2020

OVERVIEW

Olumiant, an inhibitor of the Janus kinases (JAK) pathways, is indicated for the treatment of rheumatoid arthritis in adults with moderate to severe active disease who have had an inadequate response to one or more tumor necrosis factor inhibitors.[1] It is a targeted synthetic disease-modifying antirheumatic drugs (DMARD) that may be used either as monotherapy or in combination with MTX or other conventional synthetic DMARDs. Olumiant is not recommended for use in combination with other JAK inhibitors, or in combination with biologics or potent immunosuppressants such as azathioprine or cyclosporine.

Guidelines

Guidelines from the American College of Rheumatology (2015), updated prior to the approval of Olumiant, have tumor necrosis factor (TNF) inhibitors and non-TNF biologics, administered with or without MTX, equally positioned as a recommended therapy following a trial of a conventional synthetic DMARD (e.g.,

MTX, leflunomide, hydroxychloroquine, sulfasalazine).[4] Although Olumiant is not yet addressed, another JAK inhibitor (Xeljanz/Xeljanz XR [tofacitinib tablets, tofacitinib extended release tablets]) is not recommended for early RA; in established RA, Xeljanz/XR is most frequently recommended for patients with moderate or high disease activity despite use of multiple biologics. Guidelines for treatment of inflammatory conditions recommend assessment of response to initial therapy, most often within 3 months of initiating or changing therapy.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Olumiant. Because of the specialized skills required for evaluation and diagnosis of patients treated with Olumiant as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Olumiant to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

All reviews for use of Oluminat for COVID-19 and/or cytokine release syndrome associated with COVID-19 will be forwarded to the Medical Director.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Olumiant is recommended in those who meet the following criteria:

FDA-Approved Indications

19. Rheumatoid Arthritis. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for three months if the patient meets BOTH of the following (i and ii):

i. Patient has had a 3-month trial of at least ONE tumor necrosis factor inhibitor (TNFi) for this condition, unless intolerant; AND
Note: Refer to Appendix for examples of tumor necrosis factor inhibitors used for rheumatoid arthritis. Conventional synthetic DMARDs such as methotrexate (MTX), leflunomide, hydroxychloroquine, and sulfasalazine do not count.

ii. Olumiant is prescribed by or in consultation with a rheumatologist.

B) Patients Currently Receiving Olumiant. Approve for 3 years if the patient has had a response as determined by the prescriber.
Note: Examples of a response to therapy include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Olumiant.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Olumiant is not recommended in the following situations:

80. Concurrent Use with a Biologic or with a Targeted Synthetic DMARD. Olumiant should not be administered in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see Appendix for examples).[1] Combination therapy is generally not recommended due to a potential for a higher rate of adverse effects with combinations and lack of evidence for additive efficacy.

81. Concurrent use with Other Potent Immunosuppressants (e.g., azathioprine, cyclosporine).[1] Coadministration with other potent immunosuppressive drugs has the risk of added immunosuppression and has not been evaluated in RA. Note: This does NOT exclude use of Olumiant with MTX; Olumiant has been evaluated with background MTX or combinations of conventional synthetic DMARDs containing MTX.

82. COVID-19 (Coronavirus Disease 2019). Forward all requests to the Medical Director.
Note: This includes requests for cytokine release syndrome associated with COVID-19.

83. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

73. Oluminat® tablets [prescribing information]. Indianapolis, IN: Lilly; October 2019.
74. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol*. 2016;68(1):1-26.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	06/06/2018
Annual revision	No changes to the criteria.	06/18/2019
Selected revision	**COVID-19:** This indication (including use in cytokine release syndrome associated with COVID-19) was added to the policy as a Condition Not Recommended for Coverage. All reviews are directed to the Medical Director.	04/01/2020
Annual revision	**Rheumatoid Arthritis:** Examples of tumor necrosis factor inhibitors for Rheumatoid Arthritis were moved to be included in the Appendix (previously listed in a Note in the criteria section).	07/01/2020

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, PJIA, PsO, PsA, RA, SJIA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: PJIA, PSA, RA
		IV formulation: PJIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Ilaris (canakinumab SC injection**)**	Inhibition of IL-1β	SJIA
Kineret® (anakinra SC injection)	Inhibition of IL-1	RA, SJIA^
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; PJIA – Polyarticular juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; SJIA – Systemic juvenile idiopathic arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; ^ Off-label use of SJIA supported in guidelines; DMARDs – Disease-modifying antirheumatic drugs.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Orencia Intravenous Prior Authorization Policy
- Orencia® (abatacept for intravenous infusion)

REVIEW DATE: 06/17/2020

OVERVIEW

Orencia intravenous, a selective T-cell costimulation modulator, is indicated for the following uses:

- **Rheumatoid arthritis**, for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely disease. In RA, Orencia intravenous may be used as monotherapy or concomitantly with disease-modifying antirheumatic drugs (DMARDs) other than tumor necrosis factor inhibitors (TNFis).
- **Juvenile idiopathic arthritis**, for reducing signs and symptoms in pediatric patients ≥ 2 years of age with moderately to severely active polyarticular disease. In juvenile idiopathic arthritis, Orencia intravenous may be used alone or in combination with methotrexate (MTX).
- **Psoriatic arthritis**, in adults with active disease.

Orencia should not be administered concomitantly with TNFis and is not recommended for use concomitantly with other biologics for rheumatoid arthritis. Orencia is available as an intravenous infusion that is dosed on body weight. There is also a subcutaneous injection available in prefilled syringes (50 mg, 87.5 mg, and 125 mg per syringe) to allow for use in adults and weight-based dosing in pediatric patients. Some patients initiating therapy with Orencia subcutaneous will receive a single loading dose with Orencia intravenous.

Guidelines

Orencia is addressed in guidelines for treatment of various inflammatory conditions.

- **Rheumatoid Arthritis:** Guidelines from the American College of Rheumatology (ACR) [2015] have TNFis and non-TNF biologics such as Orencia, administered with or without methotrexate, equally positioned as a recommended therapy following a trial of a conventional synthetic DMARD (e.g., methotrexate, leflunomide, hydroxychloroquine, sulfasalazine).[2]
- **Juvenile Idiopathic Arthritis:** Guidelines (2019) list biologics among the treatment options for subsequent therapy in patients with polyarthritis.[3] Initial therapy with a biologic may be considered for patients with risk factors and involvement of high-risk joints (e.g., cervical spine, wrist, or hip), high disease activity, and/or those judged to be at high risk of disabling joint damage. In patients with active sacroiliitis or enthesitis despite nonsteroidal anti-inflammatory drug, a TNFi is recommended.
- **Psoriatic Arthritis:** Guidelines from ACR (2018) recommend TNFis over other biologics for use in treatment-naïve patients with PsA and in those who were previously treated with an oral therapy.[4] However, Orencia may be considered over other biologics in patients with recurrent or serious infections.

Safety

Orencia intravenous has Warnings concerning risks of serious infection.[1] Prior to initiating therapy with Orencia, patients should be evaluated for active tuberculosis infection. If a serious infection develops, treatment with Orencia should be discontinued.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Orencia intravenous. Because of the specialized skills required for evaluation and diagnosis of patients treated with Orencia as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Orencia intravenous to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indications

2. **Rheumatoid Arthritis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **a)** Initial Therapy. Approve for 3 months if the patient meets the following criteria (i and ii):
     - i. Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND
       Note: Examples of conventional synthetic DMARDs include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already has a 3-month trial at least one biologic. Refer to Appendix for examples of biologics used for rheumatoid arthritis. These patients who have already tried a biologic are not required to "step back" and try a conventional synthetic DMARD.
     - ii. The agent is prescribed by or in consultation with a rheumatologist.
   - **b)** Patient is Currently Receiving Orencia (Intravenous or Subcutaneous). Approve for 1 year if the patient has had a response, as determined by the prescriber.
     Note: Examples of a response include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Orencia.

3. **Juvenile Idiopathic Arthritis (JIA) [or Juvenile Rheumatoid Arthritis] (regardless of type of onset).** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **a)** Initial Therapy. Approve for 3 months if the patient meets BOTH of the following criteria (i and ii):
     - i. Patient meets one of the following conditions (a, b, c, or d):
       - **a)** Patient has tried one other agent for this condition; OR
         Note: Examples of therapies which could have been tried include methotrexate, sulfasalazine, or leflunomide, and a nonsteroidal anti-inflammatory drug (NSAID). A biologic also counts as a trial of one agent for JIA. Refer to Appendix for examples of biologics used for JIA.

b) Patient will be starting on therapy concurrently with methotrexate, sulfasalazine, or leflunomide; OR

c) Patient has an absolute contraindication to methotrexate, sulfasalazine, or leflunomide; OR
Note: Examples of absolute contraindications to methotrexate include pregnancy, breast feeding, alcoholic liver disease, immunodeficiency syndrome, blood dyscrasias.

d) Patient has aggressive disease, as determined by the prescriber; AND

ii. The agent is prescribed by or in consultation with a rheumatologist.

b) Patient is Currently Receiving Orencia (Intravenous or Subcutaneous). Approve for 1 year if the patient has had a response, as determined by the prescriber.
Note: Examples of a response include improvement in limitation of motion; less joint pain or tenderness; improved function or activities of daily living; decreased duration of morning stiffness or fatigue; reduced dosage of corticosteroids; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values. The patient may not have a full response, but there should have been a recent or past response to Orencia.

4. Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

a) Initial Therapy. Approve for 3 months if prescribed by or in consultation with a rheumatologist or a dermatologist.

b) Patient is Currently Receiving Orencia (Intravenous or Subcutaneous). Approve for 1 year if the patient has responded, as determined by the prescriber.
Note: Examples of a response include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improvements in acute phase reactants (for example, C-reactive protein). The patient may not have a full response, but there should have been a recent or past response to Orencia.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Orencia intravenous is not recommended in the following situations:

84. Ankylosing Spondylitis (AS). In an open-label Phase II trial, Orencia was administered by IV infusion on Days 1, 15, 29, and every 28 days thereafter to patients with active AS.[5] Patients received a fixed dosage of Orencia of approximately 10 mg/kg based on body weight. The primary endpoint was a 40% improvement in disease activity at Week 24 in the Assessment of SpondyloArthritis international Society criteria (ASAS 40). At Week 24, the ASAS 40 was 13.3% (n = 2/15) in TNF blocker-naïve patients compared with no responses in patients who had previously failed TNF blockers (n = 15). ASAS 20 response was 26.7% (n = 4/15) in TNF blocker-naïve patients compared with 20% (n = 3/15) in those who had previously failed TNF blockers. A major response was not shown with treatment to Orencia.

85. Concurrent Use with a Biologic or with a Targeted Synthetic DMARD. Orencia IV should not be administered in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see Appendix for examples). Combination therapy is generally not recommended due to a higher rate of AEs with combinations and lack of data supportive of additional efficacy.[6-7] Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Orencia IV.

86. Inflammatory Bowel Disease (i.e., Crohn's Disease [CD], Ulcerative Colitis [UC]). In placebo-controlled trials evaluating the efficacy of Orencia IV for induction and maintenance in adults with active, moderate to severe CD (n = 451) and UC (n = 490), Orencia was no more effective than placebo.[8] Patients were randomized to Orencia 30, 10, or 3 mg/kg IV (according to body weight) or placebo and dosed at Weeks 0, 2, 4, and 8. A total of 90 patients with CD and 131 patients with UC who responded to Orencia IV induction were then randomized to Orencia 10 mg/kg IV or placebo every 4 weeks through Week 52. When used for induction of CD, 17.2%, 10.2%, and 15.5% of patients receiving Orencia 30 mg, 10 mg, and 3 mg/kg IV achieved a clinical response at Weeks 8 and 12 compared with 14.4% of patients receiving placebo (P = not significant [NS] for all comparisons). In patients with CD, response and remission at Week 52 was not significantly different between the Orencia IV and placebo treatment groups. When used as induction therapy in UC, 21.4%, 19.0%, and 20.3% of patients receiving Orencia 30 mg, 10 mg, and 3 mg/kg IV achieved a clinical response at Week 12 compared with 29.5% of patients receiving placebo (P = 0.043 for 10 mg/kg vs. placebo; other comparisons NS). At Week 52, 12.5% (n = 8/64) and 14.1% (n = 9/64) of patients with UC were in remission (P = NS) and 17.2% of patients in each treatment group (n = 11/64 for each group) had achieved a response.

87. Psoriasis. (Note: Patients with concomitant plaque psoriasis and psoriatic arthritis may be reviewed under the psoriatic arthritis criteria above.) In a multicenter, Phase I, 26-week, open-label dose-escalation study, 43 patients with stable plaque psoriasis (10% to 49% body surface area involvement) received four doses of Orencia given as a 1-hour IV infusion on Days 1, 3, 16 and 29.[9] The starting dose was 0.5 mg/kg. Four to six patients were accrued to each of eight dose levels: 0.5, 1, 2, 4, 8, 16, 25 and 50 mg/kg. A parallel control group was matched for age and overall disease severity. In all, 46% of patients on Orencia for IV infusion achieved a 50% or greater sustained improvement in clinical disease activity (Physician's Global Assessment of disease activity) compared with baseline psoriasis evaluation. Progressively greater effects were observed with the highest doses. Further studies are needed to establish safety and efficacy in plaque psoriasis.

88. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Orencia® for injection [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; March 2019.
2. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol*. 2016;68(1):1-26.
3. Ringold S, Angeles-Han ST, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for non-systemic polyarthritis, sacroiliitis, and enthesitis. *Arthritis Rheumatol*. 2019;71(6):717-734.
4. Singh JA, Guyatt G, Ogdie A, et al. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the treatment of psoriatic arthritis. *Arthritis Care Res (Hoboken)*. 2019;71(1):2-29.
5. Song IH, Heldmann F, Rudwaleit M, et al. Treatment of active ankylosing spondylitis with abatacept: an open-label, 24-week pilot study. *Ann Rheum Dis*. 2011;70(6):1108-1110.
6. Furst DE, Keystone EC, Braun J, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2011. *Ann Rheum Dis*. 2012;71 Suppl 2:i2-i45.
7. Xeljanz® tablets [prescribing information]. New York, NY: Pfizer Inc; December 2017.
8. Sandborn WJ, Colombel JF, Sands BE, et al. Abatacept for Crohn's disease and ulcerative colitis. *Gastroenterology*. 2012;143(1):62-69.e4.
9. Abrams JR, Lebwohl MG, Guzzo CA, et al. CTLA4Ig-mediated blockade of T-cell costimulation in patients with psoriasis vulgaris. *J Clin Invest*. 1999;103:1243-1252.

HISTORY

Type of Revision	Summary of Changes	Review Date

Annual revision	Throughout the policy, references to Humira, Enbrel, and Rituxan were reworded as adalimumab, etanercept, and rituximab products, respectively, with the innovator names listed as examples of these products. Renflexis and Erelzi were also added as respective examples of infliximab and etanercept products.	05/09/2018
Annual revision	**Rheumatoid Arthritis:** Truxima was added as an example of a rituximab product. To align with the Medical Policy, the duration of approval for patients currently taking Orencia IV or SC was changed to 1 year (previously was 3 years). **Juvenile Idiopathic Arthritis:** Actemra SC was added as an example of an agent which may have been previously tried. To align with the Medical Policy, the duration of approval for patients currently taking Orencia IV or SC was changed to 1 year (previously was 3 years). **Psoriatic Arthritis:** To align with the Medical Policy, the duration of approval for patients currently taking Orencia IV or SC was changed to 1 year (previously was 3 years).	06/05/2019
Annual revision	**Rheumatoid Arthritis:** Examples of conventional synthetic disease-modifying antirheumatic drugs were moved to a Note (previously listed as examples within the criteria). Examples of biologics for Rheumatoid Arthritis were moved to be included in the Appendix (previously listed in a Note in the criteria section). Examples of a response to therapy were moved to a Note (previously listed as examples within the criteria). **Juvenile Idiopathic Arthritis:** Examples of therapies that could have been tried prior to Orencia were moved to a Note (previously listed as examples within the criteria). Examples of biologics were moved to be included in the Appendix (previously listed in a Note in the criteria section). Examples of a response to therapy were moved to a Note (previously listed as examples within the criteria). For the exception applying to patients with aggressive disease, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). **Psoriatic Arthritis:** Examples of a response to therapy were moved to a Note (previously listed as examples within the criteria).	06/17/2020

APPENDIX

Products	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, PJIA, PsO, PsA, RA, SJIA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: PJIA, PSA, RA
		IV formulation: PJIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Ilaris (canakinumab SC injection**)**	Inhibition of IL-1β	SJIA
Kineret® (anakinra SC injection)	Inhibition of IL-1	RA, SJIA^
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpa, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA

Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; PJIA – Polyarticular juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; SJIA – Systemic juvenile idiopathic arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; ^ Off-label use of SJIA supported in guidelines.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Orencia Subcutaneous Prior Authorization Policy
- Orencia® (abatacept subcutaneous injection – Bristol Myers Squibb)

REVIEW DATE: 06/17/2020

OVERVIEW

Orencia subcutaneous, a selective T-cell costimulation modulator, is indicated for the following uses:

- **Rheumatoid arthritis**, for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely disease. In RA, Orencia intravenous may be used as monotherapy or concomitantly with disease-modifying antirheumatic drugs (DMARDs) other than tumor necrosis factor inhibitors (TNFis).
- **Juvenile idiopathic arthritis**, for reducing signs and symptoms in pediatric patients ≥ 2 years of age with moderately to severely active polyarticular disease. In juvenile idiopathic arthritis, Orencia intravenous may be used alone or in combination with methotrexate (MTX).
- **Psoriatic arthritis**, in adults with active disease.

Orencia should not be administered concomitantly with TNFis and is not recommended for use concomitantly with other biologics for rheumatoid arthritis. The subcutaneous injection is available in prefilled syringes containing three different doses (50 mg, 87.5 mg, and 125 mg per syringe) to allow for weight-based dosing in adults and pediatric patients. It is also available as an intravenous infusion that is dosed on body weight.

Guidelines

Orencia is addressed in guidelines for treatment of various inflammatory conditions.

- **Rheumatoid Arthritis:** Guidelines from the American College of Rheumatology (ACR) [2015] have TNFis and non-TNF biologics such as Orencia, administered with or without MTX, equally positioned as a recommended therapy following a trial of a conventional synthetic DMARD (e.g., MTX, leflunomide, hydroxychloroquine, sulfasalazine).[2]
- **Juvenile Idiopathic Arthritis:** Guidelines (ACR, 2019) list biologics among the treatment options for subsequent therapy in patients with polyarthritis.[3] Initial therapy with a biologic may be considered for patients with risk factors and involvement of high-risk joints (e.g., cervical spine, wrist, or hip), high disease activity, and/or those judged to be at high risk of disabling joint damage. In patients with active sacroiliitis or enthesitis despite nonsteroidal anti-inflammatory drug, a TNFi is recommended.

- **Psoriatic Arthritis:** Guidelines from ACR (2018) recommend TNFis over other biologics for use in treatment-naïve patients with psoriatic arthritis and in those who were previously treated with an oral therapy.[4] However, Orencia may be considered over other biologics in patients with recurrent or serious infections.

Safety

Orencia subcutaneous has Warnings concerning risks of serious infection.[1] Prior to initiating therapy with Orencia, patients should be evaluated for active tuberculosis infection. If a serious infection develops, treatment with Orencia should be discontinued.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Orencia subcutaneous injection. Because of the specialized skills required for evaluation and diagnosis of patients treated with Orencia as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Orencia subcutaneous to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indications

1. **Rheumatoid Arthritis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets BOTH of the following criteria (i and ii):
     - **i.** Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND
       Note: Examples of conventional synthetic DMARDs include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already has a 3-month trial at least one biologic. Refer to Appendix for examples of biologics used for rheumatoid arthritis. These patients who have already tried a biologic are not required to "step back" and try a conventional synthetic DMARD).
     - **ii.** The agent is prescribed by or in consultation with a rheumatologist.
   - **B)** Patient is Currently Receiving Orencia (Intravenous or Subcutaneous). Approve for 3 years if the patient has had a response, as determined by the prescriber.
     Note: Examples of a response include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Orencia.

2. **Juvenile Idiopathic Arthritis (JIA) [or Juvenile Rheumatoid Arthritis {JRA}] (regardless of type of onset)**. Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve Orencia SC for 3 months if the patient meets BOTH of the following criteria (i and ii):
     - **i.** The patient meets one of the following conditions (a, b, c, or d):
       - **m)** Patient has tried one other agent for this condition; OR
         Note: Examples of therapies which could have been tried include methotrexate, sulfasalazine, or leflunomide, and a nonsteroidal anti-inflammatory drug (NSAID). A biologic also counts as a trial of one agent for JIA. Refer to Appendix for examples of biologics used for JIA.
       - **n)** Patient will be starting on therapy concurrently with methotrexate, sulfasalazine, or leflunomide; OR
       - **o)** Patient has an absolute contraindication to methotrexate, sulfasalazine, or leflunomide; OR
         Note: Examples of absolute contraindications to methotrexate include pregnancy, breast feeding, alcoholic liver disease, immunodeficiency syndrome, blood dyscrasias.
       - **p)** Patient has aggressive disease, as determined by the prescriber; AND

ii. The agent is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Orencia (Intravenous or Subcutaneous). Approve for 3 years if the patient has had a response, as determined by the prescriber.
Note: Examples of a response include improvement in limitation of motion; less joint pain or tenderness; improved function or activities of daily living; decreased duration of morning stiffness or fatigue; reduced dosage of corticosteroids; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values. The patient may not have a full response, but there should have been a recent or past response to Orencia.

3. Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving Orencia (Intravenous or Subcutaneous). Approve for 3 years if the patient has responded, as determined by the prescriber.
Note: Examples of a response include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improvements in acute phase reactants (for example, C-reactive protein). The patient may not have a full response, but there should have been a recent or past response to Orencia.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Orencia subcutaneous is not recommended in the following situations:

89. Ankylosing Spondylitis. In an open-label Phase II trial, Orencia was administered by IV infusion on Days 1, 15, 29, and every 28 days thereafter to patients with active AS.[5] Patients received a fixed dosage of Orencia of approximately 10 mg/kg based on body weight. The primary endpoint was a 40% improvement in disease activity at Week 24 in the Assessment of SpondyloArthritis international Society criteria (ASAS 40). At Week 24, the ASAS 40 was 13.3% (n = 2/15) in TNF blocker-naïve patients compared with no responses in patients who had previously failed TNF blockers (n = 15). ASAS 20 response was 26.7% (n = 4/15) in TNF blocker-naïve patients compared with 20% (n = 3/15) in those who had previously failed TNF blockers. A major response was not shown with treatment to Orencia.

90. Concurrent Use with a Biologic or with a Targeted Synthetic DMARD. Orencia SC should not be administered in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see APPENDIX for examples). Combination therapy is generally not recommended due to a higher rate of AEs with combinations and lack of data supportive of additional efficacy.[6-7] Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Orencia (IV or SC).

91. Inflammatory Bowel Disease (i.e., Crohn's Disease [CD], Ulcerative Colitis [UC]). In placebo-controlled trials evaluating the efficacy of Orencia IV for induction and maintenance in adults with active, moderate to severe CD (n = 451) and UC (n = 490), Orencia was no more effective than placebo.[8] Patients were randomized to Orencia 30, 10, or 3 mg/kg IV (according to body weight) or placebo and dosed at Weeks 0, 2, 4, and 8. A total of 90 patients with CD and 131 patients with UC who responded to Orencia IV induction were then randomized to Orencia 10 mg/kg IV or placebo every 4 weeks through Week 52. When used for induction of CD, 17.2%, 10.2%, and 15.5% of patients receiving Orencia 30 mg, 10 mg, and 3 mg/kg IV achieved a clinical response at Weeks 8 and 12 compared with 14.4% of patients receiving placebo (P = not significant [NS] for all comparisons). In patients with CD, response and remission at Week 52 was not significantly different between the Orencia IV and

placebo treatment groups. When used as induction therapy in UC, 21.4%, 19.0%, and 20.3% of patients receiving Orencia 30 mg, 10 mg, and 3 mg/kg IV achieved a clinical response at Week 12 compared with 29.5% of patients receiving placebo (P = 0.043 for 10 mg/kg vs. placebo; other comparisons NS). At Week 52, 12.5% (n = 8/64) and 14.1% (n = 9/64) of patients with UC were in remission (P = NS) and 17.2% of patients in each treatment group (n = 11/64 for each group) had achieved a response.

92. Psoriasis. (Note: Patients with concomitant plaque psoriasis and psoriatic arthritis may be reviewed under the psoriatic arthritis criteria above.) In the pivotal trial evaluating Orencia SC for PsA, there was not a significant difference at Week 24 in PASI 50 response vs. placebo ± csDMARD (27% vs. 20% with placebo ± csDMARD; P = not significant).[10] In a multicenter, Phase I, 26-week, open-label dose-escalation study, 43 patients with stable plaque psoriasis (10% to 49% body surface area involvement) received four doses of Orencia given as a 1-hour IV infusion on Days 1, 3, 16 and 29.[9] The starting dose was 0.5 mg/kg. Four to six patients were accrued to each of eight dose levels: 0.5, 1, 2, 4, 8, 16, 25 and 50 mg/kg. A parallel control group was matched for age and overall disease severity. In all, 46% of patients on Orencia for IV infusion achieved a 50% or greater sustained improvement in clinical disease activity (Physician's Global Assessment of disease activity) compared with baseline psoriasis evaluation. Progressively greater effects were observed with the highest doses. Further studies are needed to establish safety and efficacy in plaque psoriasis.

93. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	Throughout the policy, references to Humira, Enbrel, and Rituxan were reworded as adalimumab, etanercept, and rituximab products, respectively, with the innovator names listed as examples of these products. Renflexis and Erelzi were also added as respective examples of infliximab and etanercept products.	05/09/2018
Annual revision	**Rheumatoid Arthritis:** Truxima was added as an example of a rituximab product. **Juvenile Idiopathic Arthritis:** Actemra SC was added as an example of an agent which may have been previously tried.	06/05/2019
Annual revision	**Rheumatoid Arthritis:** Examples of conventional synthetic disease-modifying antirheumatic drugs were moved to a Note (previously listed as examples within the criteria). Examples of biologics for Rheumatoid Arthritis were moved to be included in the Appendix (previously listed in a Note in the criteria section). Examples of a response to therapy were moved to a Note (previously listed as examples within the criteria). **Juvenile Idiopathic Arthritis:** Examples of therapies that could have been tried prior to Orencia were moved to a Note (previously listed as examples within the criteria). Examples of biologics were moved to be included in the Appendix (previously listed in a Note in the criteria section). Examples of a response to therapy were moved to a Note (previously listed as examples within the criteria). For the exception applying to patients with aggressive disease, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). **Psoriatic Arthritis:** Examples of a response to therapy were moved to a Note (previously listed as examples within the criteria).	06/17/2020

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, PJIA, PsO, PsA, RA, SJIA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: PJIA, PSA, RA
		IV formulation: PJIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Ilaris (canakinumab SC injection**)**	Inhibition of IL-1β	SJIA
Kineret® (anakinra SC injection)	Inhibition of IL-1	RA, SJIA^
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; PJIA – Polyarticular juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; SJIA – Systemic juvenile idiopathic arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; ^ Off-label use of SJIA supported in guidelines.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Otezla® (apremilast tablets – Amgen)

DATE REVIEWED: 04/29/2020

OVERVIEW

Otezla, an oral phosphodiesterase 4 (PDE4) inhibitor, is indicated for the following indications:

1. Psoriatic arthritis (PsA) in adults; and
2. Plaque psoriasis, in moderate to severe disease in patients who are candidates for phototherapy or systemic therapy; and

3. Behcet's disease, in adults with oral ulcers.[1]

Disease Overview

PDE4 regulates immune and inflammatory processes through control of intracellular cAMP levels and downstream protein kinase A pathways. The production of a number of key inflammatory cytokines is affected by PDE4 including interferon (IFN)γ, tumor necrosis factor (TNF)α, interleukin (IL)-12, and IL-23, thus shaping the immune response.[2] Otezla is a targeted synthetic disease-modifying anti-rheumatic drug (DMARD) that specifically targets intracellular PDE4 and, therefore, has an inhibitory effect on multiple cytokines involved in the inflammatory process.[2-3]

Guidelines

Joint guidelines from the American Academy of Dermatology (AAD) and National Psoriasis Medical Board (2020) have been published for management of psoriasis with systemic nonbiologic therapies.[8] These guidelines list Otezla as a monotherapy treatment option for patients with moderate to severe plaque psoriasis. For treatment of moderate to severe psoriasis in adults, Otezla has a similar level of evidence and strength of recommendations as methotrexate. Additionally, data support use of MTX in combination with other systemic therapies for psoriasis,[4,8] whereas there is no strong evidence supporting combination use of Otezla with other systemic therapies or with phototherapy.[4] Guidelines from the American College of Rheumatology (ACR) [2019] recommend TNF inhibitors over other biologics and Otezla for use in treatment-naïve patients with PsA and in those who were previously treated with an oral therapy.[6]

EULAR recommendations for the management of Behcet's disease (2018) mention Otezla as a treatment option for Behcet's disease with mucocutaneous involvement.[7] Other options include topical steroids, colchicine, azathioprine, thalidomide, interferon-alpha, and TNFis. TNFis are also listed among the therapeutic options for patients who present with eye involvement, refractory venous thrombosis, arterial involvement, refractory/severe gastrointestinal involvement, nervous system involvement, and/or joint involvement.

Safety

Warnings/Precautions for Otezla include depression, weight decrease, and drug interactions with strong cytochrome P450 inducers. The most commonly observed adverse events (AEs) [incidence ≥ 5%] were diarrhea, nausea, and headache.[1] Of note, Otezla does not have Warnings regarding serious infection and malignancy, which are listed for the biologic DMARDs approved for PsA, nor does Otezla have warnings for organ toxicity and laboratory monitoring that are noted with methotrexate (MTX) and leflunomide.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Otezla. Because of the specialized skills required for evaluation and diagnosis of patients treated with Otezla as well as the monitoring required for AEs and long-term efficacy, initial approval requires Otezla to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Otezla is recommended in those who meet the following criteria:

FDA-Approved Indications

20. Plaque Psoriasis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets ALL of the following criteria (i, ii, and iii):

i. The patient is an adult greater than or equal to 18 years of age; AND

ii. The patient meets ONE of the following conditions (a or b):

a) The patient has tried at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant.
Note: Examples of traditional systemic agents for psoriasis include methotrexate (MTX), cyclosporine, acitretin tablets, or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already had a 3-month trial or previous intolerance to at least one biologic. Refer to Appendix for examples of biologics used for plaque psoriasis. These patients who have already tried a biologic for psoriasis are not required to "step back" and try a traditional systemic agent for psoriasis); OR

b) The patient has a contraindication to methotrexate (MTX), as determined by the prescriber; AND

iii. Otezla is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Otezla. Approve for 3 years if the patient meets BOTH of the following conditions (i and ii):

i. The patient has already received at least 4 months of therapy with Otezla.
Note: Patients who have received < 4 months of therapy or those who are restarting therapy with Otezla should be considered under criterion 1A (Plaque Psoriasis, initial therapy); AND

ii. The patient has had a response, as determined by the prescriber.
Note: There may not be a full response by Month 4, but there should be some response.

21. Psoriatic Arthritis (PsA). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets the BOTH of following (i and ii):

i. *The patient is an adult greater than or equal to 18 years of age; AND*

ii. Otezla is prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving Otezla. Approve for 3 years if the patient meets BOTH of the following conditions (i and ii):

i. The patient has already received at least 4 months of therapy with Otezla.
Note: Patients who have received < 4 months of therapy or those who are restarting therapy with Otezla should be considered under criterion 2A [PsA, initial therapy]); AND

ii. The patient has had a response, as determined by the prescriber.

Note: Examples of a response to therapy include: less joint pain, morning stiffness, or fatigue; improved function or activities of daily living, decreased soft tissue swelling in joints or tendon sheaths, improvements in acute phase reactants [for example, C-reactive protein]).

3. **Behcet's Disease.** Approve for the duration noted if the patient meets the following criteria (A or B):
   - **A)** Initial Therapy. Approve for 4 months if the patient meets ALL of the following (i, ii, iii, and iv):
     - **i.** The patient is an adult greater than or equal to 18 years of age; AND
     - **ii.** The patient has oral ulcers or other mucocutaneous involvement; AND
     - **iii.** The patient has tried at least ONE other systemic therapy.
       Note: Examples of systemic therapies include colchicine, systemic corticosteroids, azathioprine, thalidomide, interferon alpha, tumor necrosis factor inhibitors (e.g., adalimumab [Humira], etanercept [Enbrel], certolizumab pegol [Cimzia], golimumab [Simponi/Aria], or infliximab products [Inflectra, Remicade, Renflexis]); AND
     - **iv.** Otezla is prescribed by or in consultation with a rheumatologist or dermatologist.
   - **B)** Patient is Currently Receiving Otezla. Approve for 1 year if the patient is currently taking Otezla for ≥ 120 days and has responded to therapy, as determined by the prescriber.
     Note: Examples of a response to therapy include: a decrease in the number/frequency of oral and/or genital ulcers. Patients who have received < 4 months of therapy or those who are restarting therapy with Otezla should be considered under criterion 3A (Behcet's disease, initial therapy).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Otezla has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

94. **Ankylosing Spondylitis (AS).** Current evidence does not support use of Otezla in AS. In a published double-blind, placebo-controlled Phase II study, patients (n = 38) were randomized in a 1:1 ratio to treatment with Otezla 30 mg BID or placebo.[13] At Week 12, there was not a statistically significant change from baseline compared with placebo in multiple endpoints, including the Bath Ankylosing Spondylitis Disease Activity Index, Functional Index, Global Score, or Metrology Index (BASDAI, BASFI, BAS-G, or BASMI), the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), or night pain scores.

95. **Concurrent Use with a Biologic or with a Targeted Synthetic DMARD.** Otezla is a small molecule that specifically targets intracellular PDE4 and has an inhibitory effect on multiple cytokines involved in the inflammatory process, including TNF, IFNγ, IL-12, and IL-23.[2-3] Co-administration of Otezla with a biologic or another targeted synthetic DMARD (see Appendix for examples) has the risk of added immunosuppression and has not been evaluated. Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Otezla.

96. **Rheumatoid Arthritis (RA).** Current evidence does not support use of Otezla in RA. A multicenter, double-blind, Phase II study (n = 237) randomized patients in a 1:1:1 ratio to treatment with Otezla 20 mg BID, Otezla 30 mg BID, or placebo.[14] All patients were required to take a stable dose of MTX throughout the study. At Week 16, a similar proportion of patients in all treatment groups achieved an American College of Rheumatology (ACR) 20 response (28%, 34%, and 35%, respectively). At Week 16, patients who were non-responders, defined as patients with a swollen joint count and tender joint count that had not improved by at least 20%, were required to enter early escape (patients who were receiving placebo were transitioned to Otezla 20 mg BID and patients receiving Otezla continued on

the assigned therapy for an additional year). At Week 24, all patients who received placebo were similarly transitioned to Otezla. At Weeks 24 and 52, both doses of Otezla were associated with generally similar changes versus placebo, including ACR 20, ACR 50, and ACR 70. A subset of patients underwent magnetic resonance imaging (MRI) evaluation; however, no significant difference in response rates was observed at Week 16. The study was terminated early; data were not analyzed at Year 2 as originally planned.

97. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual revision	Throughout the policy, references to Humira, Enbrel, and Remicade were reworded as adalimumab, etanercept, and infliximab products, respectively, with the innovator names listed as examples of these products. Erelzi was added as an example of an etanercept product and Renflexis and Inflectra were added as examples of infliximab products. Ilumya, Siliq, Tremfya were added as examples of biologics that may have been previously tried for psoriasis. Simponi Aria and Taltz were added as examples of biologics that may have been previously tried for psoriatic arthritis. To align with updated EULAR guidelines for Behcet's disease, add that the requirement that the patient has mucocutaneous involvement. As a result of this change, update the criterion which requires a specialist to be involved in care (remove ophthalmologist, gastroenterologist, or neurologist and add obstetrician and gynecologist). To further align with guidelines, specify that a TNFi must have been previously tried (previously required any biologic). Since approval condition for Patients Established on Otezla for ≥ 120 days only applies to Behcet's disease, move directly under this condition. Shorten initial approval to 4 months (previously 1 year) and require a response to therapy for continuation of therapy.	06/27/2018
Annual revision	**Plaque Psoriasis and Psoriatic Arthritis:** When a response to therapy is required for patients continuing therapy, wording was changed to be according to the prescriber (previously worded as prescribing physician).	07/17/2019
Selected revision	**Behcet's disease:** Move to FDA-Approved Indications (previously listed under Other Use with Supportive Evidence). To align with the approval condition, revise criteria to include adults ≥ 18 years of age. Coverage criteria was expanded to specify for patients with oral ulcers or other mucocutaneous involvement (previously listed as mucocutaneous involvement without any age limitation). To align with the approval condition, remove obstetrician and gynecologist from the specialists who may be consulted prior to prescribing Otezla. To align with pivotal study population, change criteria to require previous use of another systemic agent (previously specifically required a TNFi, unless exception criteria were met). **Psoriatic Arthritis:** To align with the labeling, limit initial approval to adults ≥ 18 years of age with psoriatic arthritis.	07/31/2019
Early annual revision	**Plaque Psoriasis:** Examples of traditional systemic agents were moved to a Note (previously listed as examples within the criteria). Examples of biologics for plaque psoriasis were moved to be included in the Appendix (previously listed in a Note in the criteria section). For the exception applying to patients with a contraindication to methotrexate, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). **Psoriatic Arthritis:** The criterion that requires a 3-month trial or intolerance to a conventional synthetic disease-modifying antirheumatic drug was removed from the policy.	04/29/2020

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, PJIA, PsO, PsA, RA, SJIA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: PJIA, PSA, RA
		IV formulation: PJIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Ilaris (canakinumab SC injection**)**	Inhibition of IL-1β	SJIA
Kineret® (anakinra SC injection)	Inhibition of IL-1	RA, SJIA^
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; PJIA – Polyarticular juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; SJIA – Systemic juvenile idiopathic arthritis; UC – Ulcerative colitis; ^ Off-label use of SJIA supported in guidelines.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Rinvoq Prior Authorization Policy

- Rinvoq® (upadacitinib extended-release tablets – AbbVie)

REVIEW DATE: 08/26/2020

OVERVIEW

Rinvoq is a Janus kinase inhibitor (JAKi).[1] It is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate, either as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying

antirheumatic drugs (DMARDs). Rinvoq is not recommended for use in combination with other JAKis, biologics, or potent immunosuppressants such as azathioprine or cyclosporine.

Across the pivotal studies, response to Rinvoq was assessed at Week 12.

Guidelines

Guidelines from the American College of Rheumatology (ACR) [2015], updated prior to the approval of Rinvoq, have tumor necrosis factor (TNF) inhibitors and non-TNF biologics, administered with or without methotrexate, equally positioned as a recommended therapy following a trial of a conventional synthetic DMARD (e.g., methotrexate leflunomide, hydroxychloroquine, sulfasalazine).[2] Although Rinvoq and Olumiant (baricitinib tablets) [another approved JAKi] are not yet addressed, another JAKi (Xeljanz/Xeljanz XR [tofacitinib tablets, tofacitinib extended release tablets]) is not recommended for early rheumatoid arthrits in established RA, Xeljanz/XR is most frequently recommended for patients with moderate or high disease activity despite use of multiple biologics.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Rinvoq. Because of the specialized skills required for evaluation and diagnosis of patients treated with Rinvoq as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Rinvoq to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

All reviews for use of Rinvoq for COVID-19 and/or cytokine release syndrome associated with COVID-19 will be forwarded to the Medical Director.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rinvoq is recommended in those who meet the following criteria:

FDA-Approved Indications

22. Rheumatoid Arthritis. Approve Rinvoq for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND

Note: Examples include methotrexate [oral or injectable], leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already had a 3-month trial of at least one biologic. Refer to Appendix for examples of biologics used for rheumatoid arthritis. These patients who have already tried a biologic for RA are not required to "step back" and try a conventional synthetic DMARD.

iii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Rinvoq. Approve for 3 years if the patient has had a response, as determined by the prescriber.

Note: Examples of a response to therapy include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Rinvoq.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rinvoq is not recommended in the following situations:

98. Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD). Rinvoq should not be administered in combination with a biologic used for an inflammatory condition (see Appendix for examples).[1] Combination therapy is generally not recommended due to a potential for a higher rate of adverse effects with combinations and lack of evidence supporting additive efficacy. There are no data evaluating combination of Rinvoq with other targeted synthetic DMARD (e.g., Otezla [apremilast tablets], Xeljanz/XR [tofacitinib tablets/extended-release tablets], Olumiant [baricitinib tablets]); therefore, safety and efficacy of this combination is unknown.

99. Concurrent use with Other Potent Immunosuppressants (e.g., azathioprine, cyclosporine).[1] Coadministration with other potent immunosuppressive drugs has the risk of added immunosuppression and has not been evaluated in rheumatoid arthritis. Note: This does NOT exclude use of Rinvoq with methotrexate. Rinvoq has been evaluated with background methotrexate and other conventional synthetic DMARDs.

100. COVID-19 (Coronavirus Disease 2019). Forward all requests to the Medical Director.
Note: This includes requests for cytokine release syndrome associated with COVID-19.

101. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/21/2019
Selected revision	**COVID-19:** This indication (including use in cytokine release syndrome associated with COVID-19) was added to the policy as a Condition Not Recommended for Coverage. All reviews are directed to the Medical Director.	04/01/2020
Annual revision	**Rheumatoid Arthritis:** Examples of biologics for rheumatoid arthritis were moved to be included in the Appendix (previously listed in a Note in the criteria section).	08/26/2020

APPENDIX

Biologic	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic Disease-Modifying Antirheumatic Drugs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous; PJIA – Polyarticular juvenile idiopathic arthritis; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; JAK – Janus kinase.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Siliq™ (brodalumab for subcutaneous injection – Valeant Pharmaceuticals)

DATE REVIEWED: 04/08/2020

OVERVIEW

Siliq is indicated for treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.[1] In plaque psoriasis, the recommended dose is 210 mg subcutaneously (SC) at Week 0, 1, and 2 followed by 210 mg once every 2 weeks (Q2W). Consider discontinuing if an adequate response has not been achieved after 12 to 16 weeks; continued treatment is unlikely to result in greater success. Siliq is intended for use under the guidance and supervision of a physician. Those trained in SC injection technique may self-inject when deemed appropriate.

Disease Overview

IL-17A is a naturally occurring cytokine involved in normal inflammatory and immune responses. However, levels of IL-17A are elevated in psoriatic plaques.[1] Siliq is a human monoclonal immunoglobulin G (IgG)2 antibody which selectively binds to interleukin (IL)-17RA and inhibits its interaction with cytokines IL-17A, IL-17-F, IL-17C, IL-17A/F heterodimer, and IL-25. By blocking IL-17RA, Siliq inhibits IL-17 cytokine-induced responses, including the release of pro-inflammatory cytokines and chemokines involved in the inflammatory process.

Guidelines

Joint guidelines from the American Academy of Dermatology (AAD) and National Psoriasis Medical Board (2019) have been published for management of psoriasis with biologics.[2] These guidelines list Siliq as a monotherapy treatment option for patients with moderate to severe plaque psoriasis. Guidelines from the European Dermatology Forum (EDF) [2015] recommend biologics (i.e., etanercept, adalimumab, infliximab, Stelara SC) as second-line therapy for induction and long-term treatment if phototherapy and conventional systemic agents have failed, are contraindicated, or are not tolerated.[3]

Safety

Siliq has a Boxed Warning, Risk Evaluation and Mitigation Strategy (REMS) program, and limited distribution program due to risks of suicidal ideation and behavior. The REMS program requires prescribers and pharmacies to be certified to prescribe and/or dispense Siliq.[4] Patients must sign a patient-prescriber agreement form and be aware of the need to seek medical attention for any new/worsening suicidal thoughts or behavior, depression, anxiety, or mood changes. Siliq is also contraindicated in Crohn's disease.[1] Other Warnings/Precautions include infections, risk for latent tuberculosis reactivation, and vaccinations.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Siliq. Because of the specialized skills required for evaluation and diagnosis of patients treated with Siliq as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Siliq to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Siliq is recommended in those who meet the following criteria:

FDA-Approved Indications

J) Plaque Psoriasis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following criteria (i, ii, and iii):

i. The patient is ≥ 18 years of age; AND

ii. The patient meets ONE of the following conditions (a or b):

a) The patient has tried at least at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant.

Note: Examples of traditional systemic agents for psoriasis include methotrexate (MTX), cyclosporine, acitretin tablets, or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already had a 3-month trial or previous intolerance to at least one biologic. Refer to **Appendix** for examples of biologics used for plaque psoriasis. These patients who have already tried a biologic for psoriasis are not required to "step back" and try a traditional systemic agent for psoriasis; OR

b) The patient has a contraindication to methotrexate (MTX), as determined by the prescriber; AND

iii. Siliq is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Siliq. Approve for 3 years if the patient has responded, as determined by the prescriber.

Note: The patient may not have a full response, but there should have been a recent or past response to Siliq.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Siliq has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

102. Concurrent Use with other Biologics or with Targeted Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs). Siliq should not be administered in combination with a biologic used for an inflammatory condition (see Appendix for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMRADs has a potential for a higher rate of adverse effects and lack controlled trial data in support of additive efficacy.[5-6] Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Siliq.

103. Crohn's Disease. Siliq is contraindicated in patients with Crohn's disease.[1] There is a published Phase II study evaluating Siliq in Crohn's disease (n = 130) that was terminated early due to a disproportionate number of worsening Crohn's disease and lack of efficacy.[7]

104. Rheumatoid Arthritis. Efficacy has not been established. A published Phase II study (n = 252) did not demonstrate improvement in American College of Rheumatology (ACR) 20/50/70 responses with Siliq vs. placebo for treatment of rheumatoid arthritis in patients who had previously failed methotrexate.[8]

105. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual revision	References to Humira and Enbrel were reworded as adalimumab and etanercept products, respectively, with the innovator names listed as examples of these products. Renflexis and Erelzi were also added as respective examples of infliximab and etanercept products. Ilumya and Tremfya were added as examples of biologics that a patient may have previously tried for plaque psoriasis.	04/04/2018
Annual revision	**Plaque Psoriasis:** Add Cimzia to the list of biologics which may have been tried prior to approval of Siliq.	04/10/2019
Annual revision	**Plaque Psoriasis:** For the exception applying to patients with a contraindication to methotrexate, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). Examples of traditional systemic agents were moved to a Note in the criteria section. Examples of biologics for psoriasis were moved to be included in the Appendix (previously listed in a Note in the criteria section). Explanation that the patient may not have a full response, but there should have been a recent or past response to Siliq was moved to a Note within the criteria.	04/08/2020

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, PJIA, PsO, PsA, RA, SJIA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: PJIA, PSA, RA
		IV formulation: PJIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Ilaris (canakinumab SC injection**)**	Inhibition of IL-1β	SJIA
Kineret® (anakinra SC injection)	Inhibition of IL-1	RA, SJIA^
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; PJIA – Polyarticular juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; SJIA – Systemic juvenile idiopathic arthritis; UC – Ulcerative colitis; ^ Off-label use of SJIA supported in guidelines.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Simponi Aria Prior Authorization Policy

- Simponi Aria® (golimumab injection, for intravenous infusion)

REVIEW DATE: 10/07/2020

OVERVIEW

Simponi Aria is a tumor necrosis factor inhibitor (TNFi) indicated for the following conditions:[1]

- **Ankylosing spondylitis**, in adults with active disease.
- **Polyarticular juvenile idiopathic arthritis**, in patients ≥ 2 years of age with active disease.
- **Psoriatic arthritis**, in patients ≥ 2 years of age with active disease.

- **Rheumatoid arthritis**, in combination with methotrexate for treatment of adults with moderately to severely active disease.

Simponi Aria is administered by intravenous infusion by a healthcare professional. Efficacy has not been established for patients switching between the Simponi Aria and Simponi subcutaneous.

Guidelines

TNFis feature prominently in guidelines for treatment of inflammatory conditions.

- **Spondyloarthritis:** Guidelines for ankylosing spondylitis and non-radiographic axial spondyloarthritis are published by the American College of Rheumatology (ACR)/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (2019).[2] Following primary nonresponse to a TNFi, an interleukin (IL)-17 blocker is recommended; however, if the patient is a secondary nonresponder, a second TNFi is recommended over switching out of the class. In patients with a contraindication to a TNFi, use of an IL-17 blocker is recommended over traditional oral agents such as methotrexate or sulfasalazine.
- **Juvenile Idiopathic Arthritis (JIA):** Simponi (golimumab, route not specified) is among the TNFis recommended in the American College of Rheumatology (ACR)/Arthritis Foundation guidelines for the treatment of JIA (2019) specific to juvenile non-systemic polyarthritis, sacroiliitis, and enthesitis.[4] TNFis are the biologics recommended for polyarthritis, sacroiliitis, enthesitis. Actemra® (tocilizumab intravenous, tocilizumab subcutaneous) and Orencia® (abatacept intravenous, abatacept intravenous) are also among the biologics recommended for polyarthritis. Biologics are recommended following other therapies (e.g., following a conventional synthetic disease-modifying antirheumatic drug [DMARD] for active polyarthritis or following a nonsteroidal anti-inflammatory drug [NSAID] for active JIA with sacroiliitis or enthesitis). However, there are situations where initial therapy with a biologic may be preferred over other conventional therapies (e.g., if there is involvement of high-risk joints such as the cervical spine, wrist, or hip; high disease activity; and/or those judged to be at high risk of disabling joint damage).
- **Psoriatic Arthritis:** Guidelines from ACR (2019) recommend TNFis over other biologics for use in treatment-naïve patients with psoriatic arthritis, and in those who were previously treated with an oral therapy.[5]
- **Rheumatoid Arthritis:** Guidelines from the ACR (2015) have TNFis and non-TNF biologics, administered with or without methotrexate, equally positioned as a recommended therapy following a trial of a conventional synthetic DMARD (e.g., methotrexate, leflunomide, hydroxychloroquine, sulfasalazine).[6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Simponi Aria. Because of the specialized skills required for evaluation and diagnosis of patients treated with Simponi Aria as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Simponi Aria to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indications

1. **Ankylosing Spondylitis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if prescribed by or in consultation with a rheumatologist.
   - **B)** Patient is Currently Receiving Simponi Aria or Subcutaneous. Approve for 1 year if the patient has had a response, as determined by the prescriber.
     Note: Examples of a response to therapy include decreased pain or stiffness, improved function or activities of daily living. The patient may not have a full response, but there should have been a recent or past response to Simponi Aria or subcutaneous.

2. **Juvenile Idiopathic Arthritis (JIA) [or Juvenile Rheumatoid Arthritis] (regardless of type of onset)** [Note: This includes patients with juvenile spondyloarthropathy/active sacroiliac arthritis]. Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **C)** Initial Therapy. Approve for 3 months if the patient meets the following criteria (i and ii):
     - **iii.** Patient meets ONE of the following conditions (a or b):
       - **c)** Patient has tried one other medication for this condition; OR
         Note: Examples of other medications for JIA include methotrexate, sulfasalazine, or leflunomide, a nonsteroidal anti-inflammatory drug (NSAID) [e.g., ibuprofen, naproxen]. A previous trial of a biologic also counts as a trial of one medication. Refer to Appendix for examples of biologics used for JIA.
       - **d)** Patient has aggressive disease, as determined by the prescriber; AND
     - **iv.** The medication is prescribed by or in consultation with a rheumatologist.
   - **D)** Patient is Currently Receiving Simponi Aria or Subcutaneous. Approve for 1 year if the patient had a response as determined by the prescriber.
     Note: Examples of a response include improvement in limitation of motion, less joint pain or tenderness, decreased duration of morning stiffness or fatigue, improved function or activities of daily living, reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Simponi Aria or subcutaneous.

3. **Psoriatic Arthritis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if prescribed by or in consultation with a rheumatologist or dermatologist.
   - **B)** Patient is Currently Receiving Simponi Aria or Subcutaneous. Approve for 1 year if the patient has had a response, as determined by the prescriber.
     Note: Examples of a response to therapy include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improvements in acute phase reactants (for example, C-reactive protein). The patient may not have a full response, but there should have been a recent or past response to Simponi Aria or subcutaneous.

4. **Rheumatoid Arthritis**. Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (i and ii):

i. Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND

Note: Examples of conventional synthetic DMARDs include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already has a 3-month trial at least one biologic. Refer to Appendix for examples of biologics used for rheumatoid arthritis. These patients who have already tried a biologic for rheumatoid arthritis are not required to "step back" and try a conventional synthetic DMARD.

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Simponi Aria or Subcutaneous. Approve for 1 year if the patient has had a response, as determined by the prescriber.

Note: Examples of a response to therapy include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Simponi Aria or subcutaneous.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Simponi Aria is not recommended in the following situations:

~~7.~~ **Concurrent Use with Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Data are lacking evaluating concomitant use of Simponi Aria in combination with another biologic or with a targeted synthetic DMARD for an inflammatory condition (see Appendix for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMARDs has a potential for a higher rate of adverse events with combinations and lack controlled trial data in support of additive efficacy. Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Simponi Aria.

8. Ulcerative Colitis. Simponi subcutaneous injection is indicated for treatment of ulcerative colitis.[5] A single-dose induction study in patients with ulcerative colitis (n = 176) evaluated doses of 1 mg/kg, 2 mg/kg, and 4 mg/kg; however, enrollment was stopped due to lower than expected efficacy in the dose-ranging Phase II portion of the study.[6] Appropriate dosing of Simponi Aria in ulcerative colitis is unclear.

9. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Patients Established on Simponi Aria or Subcutaneous:** Change approval duration to 1 year (previously was 3 years) to align with Simponi Aria Medical Policy.	10/10/2018
Annual Revision	No criteria changes.	10/16/2019
Annual Revision	**Juvenile Idiopathic Arthritis:** This approval condition was added to align with the new FDA approval. Criteria approve for 3 months if prescribed by or in consultation with a rheumatologist, and if the patient has tried one other medication for this condition, or if, according to the prescriber, the patient has aggressive disease. For a patient already taking Simponi Aria or subcutaneous, criteria approve for 1 year if the patient has responded to initial therapy. **Rheumatoid Arthritis:** Examples of biologics were moved to be included in the Appendix (previously listed in a Note in the criteria section).	10/07/2020

APPENDIX

Biologic	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzaa SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic Disease-Modifying Antirheumatic Drugs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz® (tofacitinib tablets)	Inhibition of the JAK pathways	RA, PJIA, PsA, UC
Xeljanz® XR (tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic

arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous; PJIA – Polyarticular juvenile idiopathic arthritis; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; JAK – Janus kinase.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Simponi® (golimumab for subcutaneous injection – Janssen Biotech, Inc.)

DATE REVIEWED: 04/29/2020

OVERVIEW

Simponi SC is a recombinant human monoclonal antibody specific for human tumor necrosis factor alpha (TNFα).[1] It is indicated for the following uses:

- Ankylosing spondylitis (AS), for treatment of adults with active AS either alone or in combination with MTX or other non-biologic DMARDs; AND
- Psoriatic arthritis (PsA), for treatment of adults with active PsA either alone or in combination with MTX or other non-biologic disease-modifying antirheumatic drugs (DMARDs); AND
- Rheumatoid arthritis (RA), for treatment of adults with moderate to severe active RA in combination with methotrexate (MTX); AND
- Ulcerative colitis (UC), for inducing and maintaining clinical response, improving endoscopic appearance of the mucosa during induction, inducing clinical remission, and achieving and sustaining clinical remission in induction responders in adults with moderate to severe disease who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine.

Disease Overview

TNF is a naturally occurring cytokine that mediates inflammation and modulates cellular immune responses. Increased levels of TNF have been implicated in the pathology of inflammatory conditions such as inflammatory bowel disease, psoriatic arthritis, and rheumatoid arthritis (RA). Increased levels of TNF are found in the synovial fluid of patients with RA and TNF has an important role in both the pathologic inflammation and the joint destruction that are characteristic of this disease. In Crohn's disease, increased levels of TNF are found in the bowel wall in areas involved by Crohn's disease. Simponi SC neutralizes the biological activity of TNFα and inhibits binding of TNFα with its receptors.

Guidelines

TNFis feature prominently in guidelines for treatment of inflammatory conditions.

- Spondyloarthritis: Guidelines for ankylosing spondylitis and nonradiographic axial spondylitis are published by the American College of Rheumatology (ACR)/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (2019).[2] TNFis are recommended for the initial biologic. In those who are secondary nonresponders to a TNFi, a second TNFi is recommended over switching out of the class.
- Psoriatic Arthritis: Guidelines from ACR (2019) recommend TNFis over other biologics for use in treatment-naïve patients with PsA and in those who were previously treated with an oral therapy.[3]
- Rheumatoid Arthritis: Guidelines from the American College of Rheumatology (ACR) [2015] have TNF inhibitors and non-TNF biologics, administered with or without MTX, equally positioned as a recommended therapy following a trial of a conventional synthetic DMARD (e.g., MTX, leflunomide, hydroxychloroquine, sulfasalazine).[4]

- Ulcerative Colitis: Updated ACG guidelines for UC (2019) note that the following agents can be used for induction of remission in moderately to severely active disease: Uceris tablets; Oral or intravenous systemic corticosteroids Entyvio, Xeljanz, or TNFis (adalimumab, Simponi SC, infliximab).[5]

Safety

Simponi SC has Boxed Warnings concerning risks of serious infection and the risk of malignancy.[1] Prior to initiating therapy, patients should be evaluated for active tuberculosis (TB) infection; in addition, patients should be assessed for latent TB infection periodically during therapy. Patients should also be monitored for signs and symptoms of infection during and after treatment with Simponi SC; if a serious infection or sepsis develops, Simponi SC should be discontinued. Lymphoma and other malignancies have been reported in patients who have taken TNFis such as Simponi SC.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Simponi SC. Because of the specialized skills required for evaluation and diagnosis of patients treated with Simponi SC as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Simponi SC to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration listed below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Simponi SC is recommended in those who meet the following criteria:

FDA-Approved Indications

K) Ankylosing Spondylitis (AS). Approve for the duration noted if the patient meets ONE of the following conditions (A or B):

A) Initial Therapy. Approve for 3 months if prescribed by or in consultation with a rheumatologist.

B) Patients Currently Receiving Simponi (SC or Aria). Approve for 3 years if the patient has had a response, as determined by the prescriber.

Note: Examples of a response include decreased pain or stiffness and improved function or activities of daily living. The patient may not have a full response, but there should have been a recent or past response to Simponi (SC or Aria).

L) Psoriatic Arthritis (PsA). Approve for the duration noted if the patient meets ONE of the following conditions (A or B):

A) Initial Therapy. Approve for 3 months if Simponi SC is prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patients Currently Receiving Simponi (SC or Aria). Approve for 3 years if the patient has had a response as determined by the prescriber.

Note: Examples of a response include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; and improvements in acute phase reactants such as C-reactive protein (CRP). The patient may not have a full response, but there should have been a recent or past response to Simponi (SC or Aria).

M) Rheumatoid Arthritis (RA). Approve for the duration noted if the patient meets ONE of the following conditions (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following criteria (i and ii):

i. The patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months.

Note: Examples of conventional synthetic DMARDs include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already has a 3-month trial at least one biologic. Refer to Appendix for examples of biologics used for RA. These patients who have already tried a biologic for RA are not required to "step back" and try a conventional synthetic DMARD; AND

ii. Simponi SC is prescribed by or in consultation with a rheumatologist.

B) Patients Currently Receiving Simponi (SC or Aria). Approve for 3 years if the patient has had a response, as determined by the prescriber.

Note: Examples of a response include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Simponi (SC or Aria).

N) Ulcerative Colitis (UC). Approve for the duration noted if the patient meets ONE of the following conditions (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following criteria (i, ii. and iii):

i. The patient is ≥ 18 years of age; AND

ii. The patient meets ONE of the following conditions (a or b):

i. Patient has had a trial of one conventional systemic agent or a corticosteroid such as prednisone or methylprednisolone, or was intolerant to one of these agents for ulcerative colitis.

Note: Examples of systemic therapies for ulcerative colitis include 6-mercaptopurine, azathioprine, cyclosporine, and tacrolimus. An exception to this criterion can be made if the patient has already tried a biologic. These patients who have already received a biologic are not required to "step back" and try another agent. Refer to Appendix for examples of biologics used for ulcerative colitis; OR

ii. The patient meets BOTH of the following [(1) and (2)]:

1. The patient has pouchitis; AND

2. The patient has tried therapy with an antibiotic, probiotic, corticosteroid enema, or Rowasa® (mesalamine) enema.

Note: Examples of antibiotics include metronidazole and ciprofloxacin. Hydrocortisone enemas is an examples of a corticosteroid enemas; AND

iii. Simponi SC is prescribed by or in consultation with a gastroenterologist.

B) Patients Currently Receiving Simponi (SC or Aria). Approve for 3 years if the patient has had a response, as determined by the prescriber.

Note: Examples of a response include decreased stool frequency or rectal bleeding. The patient may not have a full response, but there should have been a recent or past response to Simponi (SC or Aria).

Other Uses with Supportive Evidence

O) Spondyloarthritis (SpA), Other Subtypes (e.g., undifferentiated arthritis, non-radiographic axial SpA, Reactive Arthritis [Reiter's disease]) [Note: For AS or PsA, refer to the respective criteria under FDA-approved indications]. Approve for the duration noted if ONE of the following conditions are met (A or B):

G) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following conditions (i and ii):

i. The patient meets ONE of the following (a or b):

a) The patient has arthritis primarily in the knees, ankles, elbows, wrists, hands, and/or feet AND has tried at least ONE conventional synthetic DMARD has been tried.
Note: Examples of conventional synthetic DMARDs include methotrexate (MTX), leflunomide, and sulfasalazine; OR

b) The patient has axial spondyloarthritis AND has objective signs of inflammation, defined as at least one of the following [(1) or (2)]:

(1) C-reactive protein (CRP) elevated beyond the upper limit of normal for the reporting laboratory; OR

(2) Sacroiliitis reported on magnetic resonance imaging (MRI); AND

ii. Simponi SC is prescribed by or in consultation with a rheumatologist.

H) Patients Currently Receiving Simponi (SC or Aria). Approve for 1 year if the patient has had a response, as determined by the prescriber.
Note: Examples of a response include decreased pain or stiffness and improved function or activities of daily living. The patient may not have a full response, but there should have been a recent or past response to Simponi (SC or Aria).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Simponi SC has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

10. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Simponi SC should not be administered in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see Appendix for examples). Combination therapy is generally not recommended due to a potentially higher rate of AEs with combinations and lack of data supportive of additional efficacy.[6,7] Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with an adalimumab product.

11. **Plaque Psoriasis without Psoriatic Arthritis.** Simponi SC has been studied in patients with psoriatic arthritis who had plaque psoriasis. Plaque psoriasis improved in these patients with a Psoriasis Area Severity Index (PASI)-75 being attained by 40% of patients on Simponi 50 mg SC every 4 weeks and by 58% in the Simponi 100 mg SC group at Week 14.[8] Simponi SC is indicated in patients with psoriatic arthritis, but not in patients with plaque psoriasis without psoriatic arthritis. Prospective, controlled trials are needed to determine safety and efficacy in plaque psoriasis. Other TNFα antagonists (Enbrel, Humira, and Remicade) are indicated for the treatment of plaque psoriasis.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual revision	Throughout the policy, references to Humira, Enbrel, and Rituxan were reworded as adalimumab, etanercept, and rituximab products, respectively, with the innovator names listed as examples of these products. Erelzi was added as an example of an etanercept product and Renflexis was added as an example of an infliximab product. Entyvio was added as an example of a biologic that may have been previously tried for UC. Since approval conditon for Patients Established on Simponi Aria or SC for ≥ 90 days only applies to Spondyloarthritis, move directly under this condition. For patients established on Simponi Aria or SC for spondyloarthritis, add the requirement that the patient must have responded to previous therapy, as determined by the prescriber.	06/13/2018
Selected revision	**Ulcerative colitis:** For the requirement that another agent be tried prior to Simponi SC, remove the requirement that the trial is a duration of at least 2 months (not supported in updated guidelines).	03/27/2019
Early annual revision	**Spondyloarthritis (SpA), Other Subtypes:** This off-label approval condition was reworded (previously listed as Spondyloarthritis, Subtypes Other than Ankylosing Spondylitis or Psoriatic Arthritis). There is a note which directs to criteria for FDA-approved subtypes of SpA (AS, PsA). Criteria were changed to approve for 3 months for patients starting therapy (previously was 1 year). For patients with primarily axial disease, a criterion was added to require objective signs of inflammation, defined as C-reactive protein (CRP) elevated beyond the upper limit of normal for the reporting laboratory or sacroiliitis reported on magnetic resonance imaging. For patients currently receiving therapy, examples of a response to therapy were added; the requirement that patients be on a golimumab product for ≥ 90 days was removed.	04/24/2019
Annual revision	**Ankylosing Spondylitis:** For patients continuing therapy, examples of a response were moved to a Note in the policy (previously listed in the criteria for patients continuing therapy). **Psoriatic Arthritis:** For patients continuing therapy, examples of a response were moved to a note in the policy (previously listed in the criteria for patients continuing therapy).	04/29/2020

	Rheumatoid Arthritis: Examples of conventional synthetic disease-modifying antirheumatic drugs were moved to a Note (previously listed as examples within the criteria). Examples of biologics for Rheumatoid Arthritis were moved to be included in the Appendix (previously listed in a Note in the criteria section). Examples of a response to therapy were moved to a Note (previously listed as examples within the criteria). **Ulcerative Colitis:** The requirement that the patient is an adult was moved into the criteria section for initial therapy. Criteria were clarified to define adult as a patient ≥ 18 years of age. Previously, the requirement that the patient was an adult was listed as part of the diagnosis (i.e., previously listed as Ulcerative Colitis in an adult) and applied to initial and continuation of therapy. Examples of systemic therapies were moved to a Note (previously listed as examples within the criteria). Examples of antibiotics and corticosteroid enemas were moved to a Note (previously listed as examples within the criteria). Examples of biologics for Ulcerative Colitis were moved to be included in the Appendix (previously listed in a Note in the criteria section). Examples of a response to therapy were moved to a Note (previously listed as examples within the criteria). **Spondyloarthritis (SpA), Other Subtypes:** Examples of conventional synthetic disease-modifying antirheumatic drugs were moved to a Note (previously listed as examples within the criteria). Examples of a response to therapy were moved to a Note (previously listed as examples within the criteria).	

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, PJIA, PsO, PsA, RA, SJIA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: PJIA, PSA, RA
		IV formulation: PJIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Ilaris (canakinumab SC injection**)**	Inhibition of IL-1β	SJIA
Kineret® (anakinra SC injection)	Inhibition of IL-1	RA, SJIA^
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA

Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; PJIA – Polyarticular juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; SJIA – Sytemice juvenile idiopathic arthritis; UC – Ulcerative colitis. ^ Off-label use of SJIA supported in guidelines.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Skyrizi™ (risankizumab-rzaa subcutaneous injection – Abbvie)

TAC APPROVAL DATE: 04/29/2020

OVERVIEW

Skyrizi is a humanized immunoglobulin (Ig)G monoclonal antibody.[1] It binds to interleukin (IL)-23, a naturally occurring cytokine involved in inflammatory and immune responses, that selectively binds to the p19 subunit of the IL-23 cytokine and inhibits its interaction with the IL-23 receptor. Skyrizi is indicated for treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. In plaque psoriasis, the recommended dose is 150 mg (two injections) subcutaneously (SC) at Weeks 0 and 4 and then once every 12 weeks thereafter. Skyrizi is intended for use under the guidance and supervision of a physician. A patient or care giver trained in SC injection technique may administer Skyrizi, if deemed appropriate.

Disease Overview

Although the etiology of psoriasis is not fully established, abnormal keratin formation, epidermal proliferation, activation of the immune system, and hereditary factors appear to play roles in the pathogenesis of the disease. In psoriasis, levels of IL-23p40 and IL-12/23p40 messenger RNA are upregulated but decrease with treatment. By blocking the release of proinflammatory cytokines and chemokines, Skyrizi has an inhibitory effect on the inflammatory process.

Guidelines

Joint guidelines from the American Academy of Dermatology (AAD) and National Psoriasis Medical Board (2019) have been published for management of psoriasis with biologics.[2] These guidelines list Skyrizi as a monotherapy treatment option for patients with moderate to severe plaque psoriasis. Guidelines from the European Dermatology Forum (EDF) [2015] recommend biologics (i.e., etanercept, adalimumab, infliximab, Stelara SC) as second-line therapy for induction and long-term treatment if phototherapy and conventional systemic agents have failed, are contraindicated, or are not tolerated.[3]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Skyrizi. Because of the specialized skills required for evaluation and diagnosis of patients treated with Skyrizi as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Skyrizi to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Skyrizi is recommended in those who meet the following criteria:

FDA-Approved Indications

P) Plaque Psoriasis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following criteria (i, ii, and iii):

i. The patient is an adult ≥ 18 years of age; AND

ii. The patient meets ONE of the following conditions (a or b):

c) The patient has tried at least at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant.

Note: Examples of traditional systemic agents for psoriasis include methotrexate (MTX), cyclosporine, acitretin tablets, or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already had a 3-month trial or previous intolerance to at least one biologic Refer to Appendix for examples of biologics used for psoriasis. These patients who have already tried a biologic for psoriasis are not required to "step back" and try a traditional systemic agent for psoriasis); OR

d) The patient has a contraindication to methotrexate (MTX), as determined by the prescriber; AND

iii. The agent is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Skyrizi. Approve for 3 years if the patient has responded, as determined by the prescriber.

Note: The patient may not have a full response, but there should have been a recent or past response to Skyrizi.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Skyrizi has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

106. Concurrent Use with other Biologics or with Targeted Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs). Data are lacking evaluating concomitant use of Skyrizi with another biologic or with a targeted synthetic DMARD for an inflammatory condition (see APPENDIX for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMARDs has a potential for a higher rate of adverse effects and lack controlled trial data in support of additive efficacy.[4] Note: This does NOT exclude the use of MTX (a traditional systemic agent used to treat psoriasis) in combination with Skyrizi.

107. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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101. Skyrizi™ [prescribing information]. Thousand Oaks, CA: Amgen; May 2020.
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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/24/2019
Annual revision	**Plaque Psoriasis:** Examples of traditional systemic agents were moved to a Note (previously listed as examples within the criteria). Examples of biologics for plaque psoriasis were moved to be included in the Appendix (previously listed in a Note in the criteria section). For the exception applying to patients with a contraindication to methotrexate, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician).	04/29/2020

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, PJIA, PsO, PsA, RA, SJIA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: PJIA, PSA, RA
		IV formulation: PJIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Ilaris (canakinumab SC injection**)**	Inhibition of IL-1β	SJIA
Kineret® (anakinra SC injection)	Inhibition of IL-1	RA, SJIA^
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; PJIA – Polyarticular juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; SJIA – Systemic juvenile idiopathic arthritis; UC – Ulcerative colitis; ^ Off-label use of SJIA supported in guidelines.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Stelara Intravenous Prior Authorization Policy

- Stelara® (ustekinumab intravenous infusion – Janssen Biotech)

REVIEW DATE: 09/30/2020

OVERVIEW

Stelara for intravenous infusion, is a human monoclonal antibody against the p40 subunit of the interleukin (IL)-12 and IL-23 cytokines, is indicated in patients ≥ 18 years of age with the following conditions:[1]

- **Crohn's disease**, in patients with moderate to severe active disease; AND
- **Ulcerative colitis**, in patients with moderate to severe active disease.

In Crohn's disease and ulcerative colitis, a single weight-based dose is administered by intravenous infusion. Following induction therapy with the intravenous product, the recommended maintenance is Stelara subcutaneous injection, given as a 90 mg subcutaneous injection administered 8 weeks after the initial intravenous dose, then once every 8 weeks thereafter.

Guidelines

The American College of Gastroenterology (ACG) has guidelines for Crohn's disease (2018).[2] Stelara is a treatment option in patients who have moderate to severe disease despite treatment with another agent (e.g., corticosteroid, thiopurine, methotrexate, or tumor necrosis factor inhibitors). Stelara is not addressed in the 2019 ACG guidelines for ulcerative colitis.[3] Current guidelines for ulcerative colitis from the American Gastroenterological Association (2020) include Stelara among the therapies recommended in the outpatient setting for moderate to severe disease.[4]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Stelara intravenous. Because of the specialized skills required for evaluation and diagnosis of patients treated with Stelara intravenous as well as the monitoring required for adverse events and long-term efficacy, approval requires Stelara intravenous to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 30 days, which is an adequate duration for the patient to receive one dose.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Stelara intravenous is recommended in those who meet the following criteria:

FDA-Approved Indications

8. Crohn's Disease. Approve a single dose if the patient meets the following criteria (A, B, C, and D):
- **ii.** Patient is ≥ 18 years of age; AND
- **iii.** The medication will be used as induction therapy; AND
- **iv.** Patient meets one of the following conditions (i or ii):
  - **a)** Patient has tried or is currently taking a systemic corticosteroid, or a systemic corticosteroid is contraindicated in this patient; OR
  - **b)** Patient has tried one other conventional systemic therapy for Crohn's disease; AND
    Note: Examples of other agents for Crohn's disease include azathioprine, 6-mercaptopurine , or methotrexate. A previous trial of a biologic also counts as a trial of one other agent for Crohn's disease. Refer to Appendix for examples of biologics used for Crohn's disease.
- **v.** The medication is prescribed by or in consultation with a gastroenterologist.
  Note: Patients with fistulizing Crohn's disease or Crohn's disease of the ileal pouch must meet the above criteria for Crohn's disease in adults.

9. Ulcerative Colitis. Approve a single dose if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The medication will be used as induction therapy; AND
- **C)** Patient has had a trial of one systemic agent for ulcerative colitis; AND
  Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone or methylprednisolone. A trial of a biologic also counts as a

trial of one systemic agent for UC. Refer to Appendix for examples of biologics used for ulcerative colitis.

D) The medication is prescribed by or in consultation with a gastroenterologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Stelara intravenous is not recommended in the following situations:

5. **Ankylosing Spondylitis (AS).** There are other biologic therapies indicated in AS (e.g., Cimzia, Enbrel® [etanercept SC injection], Humira, Remicade, Simponi for SC use, Cosentyx® [secukinumab SC injection]). More data are needed to demonstrate efficacy of Stelara in this condition. There is a published proof-of-concept trial evaluating Stelara in AS (TOPAS – UsTekinumab for the treatment Of Patients with active Ankylosing Spondylitis).[4] TOPAS was a prospective, open-label study evaluating Stelara 90 mg subcutaneous at Week 0, 4, and 16 in patients (n = 20) with AS. After Week 16, patients were followed through Week 28. Patients who previously failed to respond to tumor necrosis factor inhibitor (TNFi) were excluded, but patients who discontinued a TNFi for reasons other than lack of efficacy were allowed to enroll. The primary endpoint was a 40% improvement in disease activity at Week 24 according to the Assessment of SpondyloArthritis International Society (ASAS) criteria (ASAS40). Efficacy analysis was completed in the intent-to-treat population which included all patients who received at least one dose of Stelara. In all, 65% of patients (95% confidence interval [CI]: 41%, 85%; n = 13/20) achieved an ASAS40 response at Week 24. There was at least a 50% improvement of the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) achieved by 55% of patients (95% CI: 32%, 77%; n = 11/20); improvement in other secondary endpoints were also noted. However, enthesitis (measured by MASES [Maastricht AS Entheses Score] and SPARCC [SPondyloArthritis Research Consortium of Canada] enthesitis indices) and the number of swollen joints were not significantly improved at Week 24. There was a significant reduction of active inflammation on magnetic resonance imaging at Week 24 compared with baseline in sacroiliac joints.

6. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Stelara intravenous should not be administered in combination with another biologic or with a targeted synthetic DMARD for an inflammatory condition (see Appendix for examples). Combination therapy is generally not recommended due to a potential for a higher rate of adverse effects with combinations and lack of additive efficacy. Note: This does NOT exclude the use of conventional agents (e.g., methotrexate, 6-mercaptopurine, azathioprine, and sulfasalazine) in combination with Stelara intravenous.

7. **Children or Adolescents < 18 Years of Age.** Stelara intravenous is indicated in adult patients ≥ 18 years of age.[1] Efficacy and optimal dosing needs to be identified for the intravenous formulation.

8. **Plaque Psoriasis.** Stelara for subcutaneous injection is indicated for treatment of plaque psoriasis.[1] Appropriate dosing of Stelara intravenous in plaque psoriasis is unclear.

9. **Psoriatic Arthritis.** Stelara for subcutaneous injection is indicated for treatment of psoriatic arthritis.[1] Appropriate dosing of Stelara intravenous in psoriatic arthritis is unclear.

10. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	Early annual revision to align revision date with new Stelara intravenous medical policy. No changes to the criteria.	08/29/2018
Annual Revision	**Crohn's Disease:** Criteria were added to require that the patient is greater than or equal to 18 years of age, and that Stelara intravenous is being used for Induction Therapy. Previously, these requirements were part of the indication (i.e., previously, approval condition was listed as Crohn's Disease in an adult, Induction Therapy). For approvals, clarify that 30 days is adequate duration for the patient to receive a single dose.	09/11/2019
Selected Revision	**Ulcerative Colitis:** This condition was added to the policy as an FDA-approved use. Criteria approve for one dose if the patient is greater than or equal to 18 years of age and Stelara intravenous is being used for Induction Therapy, and if the patient has tried one other agent for UC. Criteria also require that Stelara intravenous is prescribed by or in consultation with a gastroenterologist.	10/23/2019
Annual Revision	**Crohn's Disease:** Examples of biologics were moved to be included in the Appendix (previously listed in a Note in the criteria section). For the criterion applying to previous therapy, wording was changed to specify this must have been a conventional systemic therapy (criteria previously required a trial of one other agent, with conventional systemic agents listed among the examples). For the criterion applying to previous corticosteroid usage, wording was changed to specify this must have been a systemic corticosteroid that was tried or contraindicated (criteria previously more generally required a trial or contraindication to a corticosteroid without specifying the route of administration). **Ulcerative Colitis:** Examples of biologics were moved to be included in the Appendix (previously listed in a Note in the criteria section).	09/30/2020

APPENDIX

Biologic	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO

Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzaa SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic Disease-Modifying Antirheumatic Drugs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous; PJIA – Polyarticular juvenile idiopathic arthritis; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; JAK – Janus kinase.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Stelara Subcutaneous Prior Authorization Policy
- Stelara® (ustekinumab subcutaneous injection – Janssen Biotech)

REVIEW DATE: 08/05/2020

OVERVIEW

Stelara subcutaneous, an interleukin-12/23 blocker, is indicated for the following uses:[1]
- **Crohn's disease**, in patients ≥ 18 years of age with moderate to severe active disease.
- **Plaque psoriasis**, in patients ≥ 6 years of age with moderate to severe disease who are candidates for phototherapy or systemic therapy.
- **Psoriatic arthritis**, in patients ≥ 18 years of age with active disease, given alone or in combination with methotrexate.
- **Ulcerative colitis**, in patients ≥ 18 years of age with moderate to severe active disease.

A weight-based dose is administered by subcutaneous injection under the supervision of a physician or by the patient or a caregiver. For each condition, the pivotal trials for Stelara subcutaneous assessed a response to therapy on or before Month 3.

Guidelines

Guidelines for the treatment of inflammatory conditions recommend use of Stelara subcutaneous.
- **Crohn's Disease:** The American College of Gastroenterology has guidelines for Crohn's disease (2018).[2] Stelara is a treatment option in patients who have moderate to severe disease despite treatment with another agent (e.g., corticosteroid, thiopurine, methotrexate, or tumor necrosis factor inhibitors).
- **Plaque Psoriasis:** Guidelines (2019) from the American Academy of Dermatology and National Psoriasis Foundation recommend Stelara as a monotherapy treatment option or in combination with other therapies for adults with moderate to severe disease.[3]
- **Psoriatic Arthritis:** Guidelines from the American College of Rheumatology (2018) recommend Stelara after other agents (e.g., tumor necrosis factor inhibitors) have been tried.[4] Stelara may be

used in patients who have active disease despite treatment with other agents, particularly in those with concomitant inflammatory bowel disease.[4]

- **Ulcerative Colitis:** Stelara is not addressed in the 2019 American College of Gastroenterology guidelines for ulcerative colitis.[5] These guidelines note that the following agents can be used for induction of remission in moderately to severely active disease: Uceris (budesonide extended-release tablets); oral or intravenous systemic corticosteroids, Entyvio (vedolizuamb intravenous infusion), Xeljanz (tofacitinib tablets, extended-release tablets), or tumor necrosis factor inhibitors (adalimumab, Simponi SC, infliximab). Guidelines from the American Gastroenterological Association (2020) recommend Stelara for moderate to severe ulcerative colitis.[6]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Stelara subcutaneous. Because of the specialized skills required for evaluation and diagnosis of patients treated with Stelara subcutaneous as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Stelara SC to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration listed below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Stelara subcutaneous is recommended in those who meet the following criteria:

FDA-Approved Indications

10. Crohn's Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

C) Initial Therapy. Approve for 3 months if the patient meets the following criteria (i, ii, iii, and iv):

vi. Patient is ≥ 18 years of age; AND

vii. Patient meets one of the following conditions (a or b):

a) The patient has tried or is currently taking corticosteroids, or corticosteroids are contraindicated in this patient; OR

b) The patient has tried one conventional systemic therapy for Crohn's disease; AND

Note: Examples of conventional systemic therapy for Crohn's disease include azathioprine, 6-mercaptopurine, or methotrexate. An exception to the requirement for a trial of or contraindication to steroids or a trial of one other conventional systemic agent can be made if the patient has already tried at least one biologic. Refer to Appendix for examples of biologics used for Crohn's disease. These patients who have already received a biologic are not required to "step back" and try another agent.

viii. According to the prescriber, the patient will receive a single induction dose with Stelara intravenous within 2 months of initiating therapy with Stelara subcutaneous; AND

ix. The agent is prescribed by or in consultation with a gastroenterologist.

D) Patient is Currently Receiving Stelara Subcutaneous. Approve for 3 years if the patient has had a response to Stelara subcutaneous, as determined by the prescriber.

Note: Examples of a response to therapy include a decrease in symptoms such as diarrhea, pain, and/or bleeding; and/or improvement in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete blood count (CBC), and/or fecal calprotectin (fCal). The patient may not have a full response, but there should have been a recent or past response to Stelara.

Note: Patients with fistulizing Crohn's disease or Crohn's disease of the ileal pouch must meet the above criteria for Crohn's disease in adults.

11. Plaque Psoriasis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following criteria (i, ii, and iii):

i. Patient is ≥ 6 years of age; AND

ii. Patient meets ONE of the following conditions (a or b):

a) Patient has tried at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR

Note: Examples of traditional systemic agents used for psoriasis include methotrexate, cyclosporine, acitretin, or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already has a 3-month trial or previous intolerance to at least one biologic. Refer to Appendix for examples of biologics used for plaque psoriasis. These patients who have already tried a biologic for psoriasis are not required to "step back" and try a traditional systemic agent for psoriasis.

b) Patient has a contraindication to methotrexate as determined by the prescriber; AND

iii. The agent is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Stelara Subcutaneous. Approve for 3 years if the patient has responded, as determined by the prescriber.

Note: The patient may not have a full response, but there should have been a recent or past response to Stelara.

12. Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving Stelara Subcutaneous. Approve for 3 years if the patient has responded, as determined by the prescriber.

Note: Examples of a response to therapy include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improvements in acute phase reactants (for example, C-reactive protein). The patient may not have a full response, but there should have been a recent or past response to Stelara.

13. Ulcerative Colitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, iii, and iv):

i. The patient ≥ to 18 years of age; AND

ii. The patient has had a trial of one systemic agent for ulcerative colitis; AND

Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone, methylprednisolone. A trial of a biologic also counts as a trial of one systemic agent for ulcerative colitis. Refer to Appendix for examples of biologics used for ulcerative colitis.

iii. According to the prescriber, the patient will receive a single induction dose with Stelara intravenous within 2 months of initiating therapy with Stelara subcutaneous; AND

iv. The agent is prescribed by or in consultation with a gastroenterologist.

B) Patient is Currently Receiving Stelara Subcutaneous. Approve for 3 years if the patient has had a response to therapy, as determined by the prescriber.

Note: Examples of a response to therapy include decreased stool frequency or rectal bleeding.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Stelara SC is not recommended in the following situations:

11. **Ankylosing Spondylitis.** There are other biologic therapies indicated in ankylosing spondylitis (e.g., Cimzia, Enbrel, Humira, Remicade, Simponi SC, Cosentyx). More data are needed to demonstrate efficacy of Stelara in this condition. There is a published proof-of-concept trial evaluating Stelara in ankylosing spondylitis.[7] TOPAS was a prospective, open-label study evaluating Stelara 90 mg at Week 0, 4, and 16 in patients (n = 20) with ankylosing spondylitis After Week 16, patients were followed through Week 28. Patients who previously failed to respond to TNF blockers were excluded, but patients who discontinued a TNF for reasons other than lack of efficacy were allowed to enroll. The primary endpoint was a 40% improvement in disease activity at Week 24 according to the Assessment of SpondyloArthritis International Society (ASAS) criteria (ASAS40). Efficacy analysis was completed in the intent-to-treat population which included all patients who received at least one dose of Stelara. In all, 65% of patients (95% confidence interval [CI]: 41%, 85%; n = 13/20) achieved an ASAS40 response at Week 24. There was at least a 50% improvement of the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) achieved by 55% of patients (95% CI: 32%, 77%; n = 11/20); improvement in other secondary endpoints were also noted. However, enthesitis (measured by MASES [Maastricht AS Entheses Score] and SPARCC [SPondyloArthritis Research Consortium of Canada] enthesitis indices) and the number of swollen joints were not significantly improved at Week 24. There was a significant reduction of active inflammation on magnetic resonance imaging at Week 24 compared with baseline in sacroiliac joints.

12. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Stelara should not be administered in combination with another biologic agent or with a targeted synthetic DMARD used for an inflammatory condition (see Appendix for examples).[8] Combination therapy is generally not recommended due to a potential for a higher rate of adverse effects with combinations and lack of additive efficacy. Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Stelara.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	**Plaque Psoriasis:** Add Ilumya and Cimzia as biologics that may have been tried prior to Stelara SC. **Conditions Not Recommended for Approval:** Remove exclusion for patients < 12 years of age (addressed in criteria). **Other:** Throughout the policy, remove criteria related to the dose (45 mg vs. 90 mg dose) approved in PA criteria (DQM now in place).	08/29/2018
Annual revision	**Crohn's Disease:** Move requirement that the patient be an adult into the criteria section for initial therapy. Further clarify that the patient must be 18 years of age or older. Previously, age was listed as part of the diagnosis without a specified age (i.e., previously listed as Crohn's disease in an adult) and applied to initial and continuation of therapy. For clarity, "according to the prescriber" was added to the criterion that requires induction with Stelara intravenous.	09/11/2019
Selected revision	**Ulcerative Colitis:** This condition was added to the policy as an FDA-approved use. Criteria approve if the patient is greater than or equal to 18 years of age, has tried one other systemic agent for UC, and the agent is prescribed by or in consultation with a gastroenterologist. Criteria also require that, according to the prescriber, the patient will receive a single induction dose with Stelara IV within 2 months of initiating therapy with Stelara SC. Initial approvals are for 3 months and continuation of therapy is for 3 years.	10/23/2019
Early annual revision	**Crohn's Disease:** Examples of biologics for Crohn's disease were moved to be included in the Appendix (previously listed in a Note in the criteria section). **Plaque Psoriasis:** To align with updated labeling, criteria were changed to approve in patients ≥ 6 years of age (previously approved in patients ≥ 12 years of age). Examples of biologics for plaque psoriasis were moved to be included in the Appendix (previously listed in a Note in the criteria section). **Ulcerative Colitis:** Examples of biologics for ulcerative colitis were moved to be included in the Appendix (previously listed in a Note in the criteria section).	08/05/2020

APPENDIX

Product	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO, PsA
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; ^ Off-label use of Kineret in JIA supported in guidelines.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Taltz® (ixekizumab for subcutaneous injection – Eli Lilly and Company)

DATE REVIEWED: 04/08/2020; selected revision 06/10/2020

OVERVIEW

Taltz, an interleukin (IL)-17A blocker, is indicated for the following uses:[1]

- **Ankylosing spondylitis**, in adults with active disease; AND
- **Non-radiographic axial spondyloarthritis**, in adults with active disease and objective signs of inflammation; AND

- **Plaque psoriasis**, in patients ≥ 6 years of age with moderate to severe disease who are candidates for systemic therapy or phototherapy; AND
- **Psoriatic arthritis**, in adults with active disease.

In the pivotal trial for non-radiographic axial spondyloarthritis, patients were required to have objective signs of inflammation, indicated by elevated C-reactive protein and/or sacroilitis on magnetic resonance imaging.

Guidelines

- **Spondyloarthritis:** Guidelines for ankylosing spondylitis and nonradiographic axial spondylitis are published by the American College of Rheumatology (ACR)/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (2019).[2] Following primary nonresponse to a TNFi, either Cosentyx or Taltz is recommended; however, if the patient is a secondary nonresponder, a second TNFi is recommended over switching out of the class. In patients with a contraindication to a TNFi, use of an IL blocker is recommended over traditional oral agents such as methotrexate or sulfasalazine.
- **Plaque Psoriasis:** Joint guidelines from the American Academy of Dermatology (AAD) and National Psoriasis Medical Board (2019) have been published for management of psoriasis with biologics.[3] These guidelines list Taltz as a monotherapy treatment option for patients with moderate to severe plaque psoriasis. Guidelines from the European Dermatology Forum (EDF) [2015] recommend biologics (i.e., etanercept, adalimumab, infliximab, Stelara SC) as second-line therapy for induction and long-term treatment if phototherapy and conventional systemic agents have failed, are contraindicated, or are not tolerated.[4]
- **Psoriatic Arthritis:** Guidelines from the American College of Rheumatology (ACR) [2019] recommend TNF inhibitors over other biologics for use in treatment-naïve patients with PsA and in those who were previously treated with an oral therapy.[5]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Taltz. Because of the specialized skills required for evaluation and diagnosis of patients treated with Taltz as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Taltz to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Taltz is recommended in those who meet the following criteria:

FDA-Approved Indications

Q) Ankylosing Spondylitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Taltz. Approve for 3 years if the patient has had a response, as determined by the prescriber.

Note: Examples of a response to therapy include decreased pain or stiffness, improved function or activities of daily living. The patient may not have a full response, but there should have been a

recent or past response to Taltz. The patient may not have a full response, but there should have been a recent or past response to Taltz.

2. Non-Radiographic Axial Spondyloarthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

C) Initial Therapy. Approve for 3 months if the patient meets BOTH of the following (i and ii):

i. The patient has objective signs of inflammation, defined as at least one of the following (a or b):

a) C-reactive protein elevated beyond the upper limit of normal for the reporting laboratory; OR

b) Sacroiliitis reported on magnetic resonance imaging; AND

ii. The agent is prescribed by or in consultation with a rheumatologist.

D) Patients Currently Receiving Taltz. Approve for 3 years if the patient has had a response, as determined by the prescriber.

Note: Examples of a response include decreased pain or stiffness, improved function or activities of daily living. The patient may not have a full response, but there should have been a recent or past response to Taltz.

R) Plaque Psoriasis. Approve Taltz for the duration noted if the patient meets ONE of the following conditions (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following criteria (i, ii, and iii):

i. The patient is ≥ 6 years of age; AND

ii. The patient meets ONE of the following conditions (a or b):

1. The patient has tried at least at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR

Note: Examples include methotrexate (MTX), cyclosporine, acitretin [Soriatane®, generics], or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already had a 3-month trial or previous intolerance to at least one biologic. Refer to **Appendix** for examples of biologics used for plaque psoriasis. These patients who have already tried a biologic for psoriasis are not required to "step back" and try a traditional systemic agent for psoriasis).

2. The patient has a contraindication to methotrexate (MTX), as determined by the prescribing physician; AND

iii. The agent is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Taltz. Approve for 3 years if the patient has responded, as determined by the prescriber.

Note: The patient may not have a full response, but there should have been a recent or past response to Taltz.

S) Psoriatic Arthritis (PsA). Approve Taltz for the duration noted if the patient meets ONE of the following conditions (A or B):

A) Initial Therapy. Approve for 3 months if prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving Taltz. Approve for 3 years if the patient has responded as determined by the prescriber.

Note: Examples of a response include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improvements in acute phase reactants [for example, C-reactive protein [CRP]). The patient may not have a full response, but there should have been a recent or past response to Taltz.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Taltz has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

108. Concurrent Use with other Biologics or with Targeted Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs). Taltz should not be administered in combination with a biologic used for an inflammatory condition (see Appendix for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMRADs has a potential for a higher rate of adverse effects and lack controlled trial data in support of additive efficacy.[6,7] Note: This does NOT exclude the use of MTX (a traditional systemic agent used to treat psoriasis) in combination with Taltz.

109. Inflammatory Bowel Disease (i.e., Crohn's disease, ulcerative colitis). Exacerbations of inflammatory bowel disease, in some cases serious, occurred in clinical trials with Taltz-treated patients.[1]

110. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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110. Otezla® tablets [prescribing information]. Summit, NJ: Celgene Corporation; July 2019.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual revision	References to Humira and Enbrel were reworded as adalimumab and etanercept products, respectively, with the innovator names listed as examples of these products. Renflexis and Erelzi were also added as respective examples of infliximab and etanercept products. Ilumya, Siliq, and Tremfya were added as examples of biologics that a patient may have previously tried for plaque psoriasis.	04/04/2018
Annual revision	**Plaque Psoriasis:** Add Cimzia to the list of biologics which may have been tried prior to approval of Taltz.	04/10/2019
Selected revision	**Ankylosing Spondylitis:** Add this new FDA-approved indication to the policy. Criteria approve for 3 months of initial therapy, if prescribed by or in consultation with a rheumatologist. For patients continuing therapy, approval is for 3 years, if patient has responded to therapy.	09/04/2019
Annual revision	**Plaque Psoriasis:** Criteria were changed to require patients be ≥ 6 years of age to receive Taltz for this indication. Previously, criteria required the patient to be an adult ≥ 18 years of age. **Conditions Not Recommended for Approval:** Patients < 18 years of age was removed from the Conditions Not Recommended for Approval.	04/08/2020

Selected revision	**Non-Radiographic Axial Spondyloarthritis:** This newly approved indication was added to the policy. Criteria approve for initial therapy for 3 months if prescribed by a rheumatologist and the patient has objective signs of inflammation, defined as C-reactive protein elevated beyond the upper limit of normal for the reporting or laboratory sacroiliitis reported on magnetic resonance imaging. For patients currently taking Taltz, criteria approve for 3 years if the patient has responded to therapy.	06/10/2020

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, PJIA, PsO, PsA, RA, SJIA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: PJIA, PSA, RA
		IV formulation: PJIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Ilaris (canakinumab SC injection**)**	Inhibition of IL-1β	SJIA
Kineret® (anakinra SC injection)	Inhibition of IL-1	RA, SJIA^
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; PJIA – Polyarticular juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; SJIA – Systemic juvenile idiopathic arthritis; UC – Ulcerative colitis; ^ Off-label use of SJIA supported in guidelines.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Tremfya Prior Authorization Policy

- Tremfya™ (guselkumab for subcutaneous injection– Janssen Biotech/Johnson & Johnson)

REVIEW DATE: 07/22/2020

OVERVIEW

Tremfya, an interleukin (IL)-23 blocker, is indicated for the following uses:[1]

- **Plaque psoriasis**, in adults with moderate to severe disease who are candidates for systemic therapy or phototherapy.

- **Psoriatic arthritis**, in adults with active disease (given ± a conventional synthetic disease-modifying antirheumatic drug).

Guidelines

Joint guidelines from the American Academy of Dermatology and National Psoriasis Medical Board (2019) have been published for management of psoriasis with biologics.[2] These guidelines list Tremfya as a monotherapy treatment option for patients with moderate to severe plaque psoriasis. It is recommended that a response to therapy be ascertained after 12 weeks of continuous therapy. Guidelines from the European Dermatology Forum (2015) recommend biologics (i.e., etanercept, adalimumab, infliximab, Stelara SC) as second-line therapy for induction and long-term treatment if phototherapy and conventional systemic agents have failed, are contraindicated, or are not tolerated.[3]

Guidelines from the American College of Rheumatology/National Psoriasis Foundation (2018) were published prior to approval of Tremfya for psoriatic arthritis. However, these guidelines generally recommend tumor necrosis factor inhibitors as the first-line treatment strategy over other biologics (e.g., IL-17 blockers, IL-12/23 inhibitor) with differing mechanisms of action.[4]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Tremfya. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tremfya as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Tremfya to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tremfya is recommended in those who meet the following criteria:

FDA-Approved Indications

T) Plaque Psoriasis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, and iii):

i. Patient is an adult ≥ 18 years of age; AND

ii. Patient meets ONE of the following conditions (a or b):

a) Patient has tried at least at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR

Note: Examples include methotrexate (MTX), cyclosporine, acitretin [Soriatane®, generics], or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already had a 3-month trial or previous intolerance to at least one biologic for this condition. (Refer to **Appendix** for examples of biologics used for psoriasis.) These patients who have already tried a biologic for psoriasis are not required to "step back" and try a traditional systemic agent for psoriasis).

b) Patient has a contraindication to methotrexate, as determined by the prescriber; AND

iii. The requested agent is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving Tremfya. Approve for 3 years if the patient has responded, as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to Tremfya.

U) Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if Tremfya is prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving Tremfya. Approve for 3 years if the patient has responded, as determined by the prescriber.

Note: Examples of a response include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improvements in acute phase reactants (for example, C-reactive protein). The patient may not have a full response, but there should have been a recent or past response to therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tremfya is not recommended in the following situations:

111. Concurrent Use with other Biologics or with Targeted Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs). Data are lacking evaluating concomitant use of Tremfya in combination with another biologic or with a targeted synthetic DMARD for an inflammatory condition (see Appendix for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMARDs has a potential for a higher rate of adverse effects and lack controlled trial data in support of additive efficacy.

Note: This does NOT exclude the use of MTX (a traditional systemic agent used to treat psoriasis) in combination with Tremfya.

112. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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114. Singh JA, Guyatt G, Ogdie A, et al. 2018 American College of Rheumatology/National Psoriasis Foundation guideline for the treatment of psoriatic arthritis. *Arthritis Rheumatol.* 2019;71(1):5-32.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	Plaque Psoriasis: • Update the list of previous therapies to include Ilumya and Cimzia. • References to Humira and Enbrel were reworded as adalimumab and etanercept products, respectively, with the innovator names listed as examples of these products. Renflexis was added as an example of an infliximab product.	08/01/2018
Annual revision	**Plaque Psoriasis:** For the exception applying to patients with a contraindication to methotrexate, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). Skyrizi was added to the list of biologics that the patient may have tried prior to Tremfya.	07/31/2019
Annual revision	**Plaque Psoriasis:** Examples of biologics for psoriasis were moved to be included in the Appendix (previously listed in a Note in the criteria section). **Psoriatic Arthritis:** This newly approved indication was added to the policy. Criteria approve for initial therapy for 3 months if prescribed by a rheumatologist or dermatologist. For patients currently taking, criteria approve for 3 years if the patient responded to therapy.	07/22/2020

APPENDIX

Biologic	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO, PsA
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; ^ Off-label use of Kineret in JIA supported in guidelines.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Xeljanz/Xeljanz XR Prior Authorization Policy

- Xeljanz®/Xeljanz XR (tofacitinib tablets, oral solution/extended-release tablets – Pfizer)

REVIEW DATE: 07/15/2020; selected revision 10/07/2020 and 03/03/2021

OVERVIEW

Xeljanz/Xeljanz XR is an inhibitor of the Janus kinases (JAK) pathways.[1] Xeljanz/XR tablets are approved for the following uses:

- **Polyarticular juvenile idiopathic arthritis**, in patients ≥ 2 years of age with active disease. Note: This indication is for Xeljanz only (not the XR formulation).

- **Psoriatic arthritis**, in adults who have had an inadequate response or intolerance to methotrexate or other disease-modifying antirheumatic drugs (DMARDs). In psoriatic arthritis, Xeljanz/Xeljanz XR should be used in combination with a conventional synthetic DMARD.
- **Rheumatoid arthritis**, in adults with moderately to severely active disease who have had an inadequate response or intolerance to methotrexate.
- **Ulcerative colitis**, in adults with moderately to severely active disease who have had an inadequate response or who are intolerant to tumor necrosis factor inhibitors (TNFis).

Xeljanz oral solution is only indicated for **polyarticular juvenile idiopathic arthritis**.

For all indications, Xeljanz/Xeljanz XR is not recommended for use in combination with biologics or potent immunosuppressants such as azathioprine or cyclosporine.

Guidelines

Guidelines for treatment of inflammatory conditions recommend assessment of response to initial therapy, most often within 3 months of initiating or changing therapy. In ulcerative colitis, the Prescribing Information recommends discontinuation of Xeljanz/Xeljanz XR if adequate therapeutic response is not achieved by Week 16.

- **Juvenile idiopathic arthritis (JIA):** Xeljanz is not addressed in the American College of Rheumatology (ACR)/Arthritis Foundation guidelines for the treatment of JIA (2019) specific to juvenile non-systemic polyarthritis, sacroiliitis, and enthesitis.[2] TNFis are the biologics recommended for polyarthritis, sacroiliitis, enthesitis. Actemra® (tocilizumab intravenous, tocilizumab subcutaneous) and Orencia® (abatacept intravenous, abatacept intravenous) are also among the biologics recommended for polyarthritis. Biologics are recommended following other therapies (e.g., following DMARDs for active polyarthritis or following a nonsteroidal anti-inflammatory drug [NSAID] for active JIA with sacroiliitis or enthesitis). However, there are situations where initial therapy with a biologic may be preferred over other conventional therapies (e.g., if there is involvement of high-risk joints such as the cervical spine, wrist, or hip; high disease activity; and/or those judged to be at high risk of disabling joint damage).
- **Psoriatic arthritis:** Guidelines from ACR (2019) recommend TNFis over other biologics and Xeljanz for use in treatment-naïve patients with psoriatic arthritis and in those who were previously treated with an oral therapy.[3]
- **Rheumatoid arthritis:** Guidelines from ACR (2015) have TNFis and non-TNF biologics, administered with or without methotrexate, equally positioned as a recommended therapy following a trial of a conventional synthetic DMARD (e.g., methotrexate, leflunomide, hydroxychloroquine, sulfasalazine).[4]
- **Ulcerative colitis:** Guidelines from the American College of Gastroenterology for UC (2019) note that the following agents can be used for induction of remission in moderately to severely active disease: Uceris tablets; Oral or intravenous systemic corticosteroids Entyvio, Xeljanz, or TNFis (adalimumab, Simponi SC, infliximab).[5] Guidelines from the American Gastroenterological Association (2020) recommend Xeljanz only after failure of or intolerance to a TNFi.[6]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Xeljanz/Xeljanz XR. Because of the specialized skills required for evaluation and diagnosis of a patient treated with Xeljanz/Xeljanz XR as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Xeljanz/Xeljanz XR to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

All reviews for use of Xeljanz/Xeljanz XR for COVID-19 and/or cytokine release syndrome associated with COVID-19 will be forwarded to the Medical Director.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xeljanz/Xeljanz XR is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Juvenile Idiopathic Arthritis (JIA) [or Juvenile Rheumatoid Arthritis] (regardless of type of onset)** [Note: This includes a patient with juvenile spondyloarthropathy/active sacroiliac arthritis]. Approve Xeljanz tablets (not the Xeljanz XR formulation) or oral solution for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets the following criteria (i and ii):
     - **i.** Patient meets ONE of the following conditions (a or b):
       - **a)** Patient has tried one other medication for this condition; OR
         Note: Examples of other medications for JIA include methotrexate, sulfasalazine, or leflunomide, a nonsteroidal anti-inflammatory drug (NSAID) [e.g., ibuprofen, naproxen]. A previous trial of a biologic also counts as a trial of one medication. Refer to Appendix for examples of biologics used for JIA.
       - **b)** Patient has aggressive disease, as determined by the prescriber; AND
     - **ii.** The medication is prescribed by or in consultation with a rheumatologist.
   - **B)** Patient is Currently Receiving Xeljanz. Approve for 3 years if the patient had a response as determined by the prescriber.
     Note: Examples of a response include improvement in limitation of motion, less joint pain or tenderness, decreased duration of morning stiffness or fatigue, improved function or activities of daily living, reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Xeljanz.

2. **Psoriatic Arthritis.** Approve Xeljanz/XR tablets (not oral solution) for the duration noted if the patient meets ONE of the following criteria (A or B):
   - A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND
       Note: Examples include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already has a 3-month trial at least one biologic. Refer to Appendix for examples of biologics used for psoriatic arthritis. A patient who has already tried a biologic is not required to "step back" and try a conventional synthetic DMARD).
     - **iii.** The medication will be used concomitantly with methotrexate or another conventional synthetic DMARD, unless contraindicated; AND
       Note: Examples of other conventional synthetic DMARDs include leflunomide and sulfasalazine.
     - **iv.** The agent is prescribed by or in consultation with a rheumatologist or a dermatologist.
   - **B)** Patient is Currently Receiving Xeljanz/Xeljanz XR. Approve for 3 years if the patient meets BOTH of the following (i and ii):
     - **i.** The medication will be used concomitantly with methotrexate or another conventional synthetic DMARD, unless contraindicated; AND

Note: Examples of other conventional synthetic DMARDs include leflunomide and sulfasalazine.

ii. Patient has responded as determined by the prescriber.
Note: Examples of a response to therapy include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improvements in acute phase reactants (for example, C-reactive protein). The patient may not have a full response, but there should have been a recent or past response to Xeljanz/Xeljanz XR.

3. Rheumatoid Arthritis. Approve Xeljanz/XR tablets (not oral solution) for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND
  Note: Examples include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already has a 3-month trial at least one biologic. Refer to Appendix for examples of biologics used for rheumatoid arthritis. A patient who have already tried a biologic is not required to "step back" and try a conventional synthetic DMARD).
- **ii.** The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Xeljanz/Xeljanz XR. Approve for 3 years if the patient has had a response, as determined by the prescriber.
Note: Examples of a response to therapy include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Xeljanz/Xeljanz XR.

4. Ulcerative Colitis. Approve Xeljanz/XR tablets (not oral solution) for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient has had a trial of at least ONE tumor necrosis factor inhibitor for ulcerative colitis; AND
  Note: Examples of a tumor necrosis factor inhibitor include an adalimumab product, an infliximab product, Simponi SC (golimumab SC injection).
- **iii.** The agent is prescribed by or in consultation with a gastroenterologist.

B) Patient is Currently Receiving Xeljanz/Xeljanz XR. Approve for 3 years if the patient has had a response, as determined by the prescriber.
Note: Examples of a response include decreased stool frequency or rectal bleeding. The patient may not have a full response, but there should have been a recent or past response to Xeljanz/ Xeljanz XR.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xeljanz/Xeljanz XR is not recommended in the following situations:

113. Concurrent Use with a Biologic or with a Targeted Synthetic DMARD. Xeljanz/XR should not be administered in combination with a biologic used for an inflammatory condition (see Appendix for examples).[1] Combination therapy is generally not recommended due to a potential for a higher rate of

adverse effects with combinations and lack of evidence supporting additive efficacy. There are no data evaluating combination of Xeljanz/XR with a targeted synthetic DMARD (e.g., Otezla); therefore, safety and efficacy of this combination is unknown.

114. Concurrent use with Other Potent Immunosuppressants (e.g., azathioprine, tacrolimus, cyclosporine, mycophenolate mofetil).[1] Coadministration with other potent immunosuppressive drugs has the risk of added immunosuppression and has not been evaluated in RA. In UC, Xeljanz is not recommended for use in combination with potent immunosuppressants such as azathioprine and cyclosporine.
Note: This does NOT exclude use of Xeljanz/Xeljanz XR with methotrexate for RA; Xeljanz/Xeljanz XR has been evaluated in patients with rheumatoid arthritis taking background methotrexate, leflunomide, or combinations of DMARDs containing methotrexate and/or leflunomide.

115. COVID-19 (Coronavirus Disease 2019). Forward all requests to the Medical Director.
Note: This includes requests for cytokine release syndrome associated with COVID-19.

116. Renal Transplantation. More data are needed. A Phase IIb study in kidney transplant patients (n = 331) found Xeljanz was equivalent to cyclosporine in preventing acute rejection.[7] However, based on Phase IIb studies, there are concerns of Epstein Barr Virus-associated post-transplant lymphoproliferative disorder (PTLD) in certain transplant patients receiving Xeljanz.[1,6]

117. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Rheumatoid arthritis:** Truxima was added as an example of a rituximab product.	06/18/2019
Selected Revision	**Ulcerative Colitis:** To align with updated labeling, revise criteria to approve if the patient has previously tried at least one tumor necrosis factor inhibitor for ulcerative colitis (previously, criteria required a trial of one systemic therapy, unless intolerant). Move the requirement that the patient is an adult into the criteria section for initial therapy. Clarify criteria to require the patient be ≥ 18 years of age. Previously, the requirement that the patient was an adult was listed as part of the diagnosis (i.e., previously listed as ulcerative colitis in an adult) and applied to initial and continuation. **Rheumatoid Arthritis:** To align with labeling, limit initial approval to adults ≥ 18 years of age.	07/31/2019

	Psoriatic Arthritis: To align with the labeling, limit initial approval to adults ≥ 18 years of age.	
Selected Revision	**Ulcerative Colitis:** Change policy to approve either Xeljanz or Xeljanz XR for this condition. Previously, only Xeljanz was able to be approved for this condition.	12/18/2019
Selected Revision	**COVID-19:** This indication (including use in cytokine release syndrome associated with COVID-19) was added to the policy as a Condition Not Recommended for Coverage. All reviews are directed to the Medical Director.	04/01/2020
Annual Revision	**Psoriatic Arthritis:** Examples of biologics for psoriatic arthritis were moved to be included in the Appendix (previously listed in a Note in the criteria section). **Rheumatoid Arthritis:** Examples of biologics for rheumatoid arthritis were moved to be included in the Appendix (previously listed in a Note in the criteria section).	07/15/2020
Selected Revision	**Juvenile Idiopathic Arthritis:** This approval condition was added to align with the new FDA approval for Xeljanz. Criteria approve Xeljanz (not the Xeljanz XR formulation) for 3 months if prescribed by or in consulation with a rheumatologist, and if the patient has tried one other medication for this condition, or if. according to the prescriber, the patient has aggressive disease. For a patient already taking Xeljanz, criteria approve for 3 years if the patient has responded to initial therapy.	10/07/2020
Selected Revision	Xeljanz oral solution was added to the policy. **Juvenile Idiopathic Arthritis:** Xeljanz solution was added as an approvable formulation for this indication.	03/03/2021

APPENDIX

Biologic	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz® (tofacitinib tablets)	Inhibition of the JAK pathways	RA, PJIA, PsA, UC
Xeljanz® XR (tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; ^ Off-label use of Kineret in JIA supported in guidelines; DMARDs – Disease-modifying antirheumatic drug.

PRIOR AUTHORIZATION POLICY

POLICY: Interferon – Actimmune® (interferon gamma-1b subcutaneous injection – Horizon Pharma)

DATE REVIEWED: 04/15/2020

OVERVIEW

Actimmune is indicated for reducing the frequency and severity of serious infections associated with chronic granulomatous disease (CGD) of patients ≥ 1 year of age.[1] Actimmune is also indicated for delaying time to disease progression age with severe, malignant osteopetrosis (SMO) of patients ≥ 1 month of age. Actimmune has shown a treatment-related enhancement of superoxide production by phagocytes and was found to enhance osteoclast function in vivo. Actimmune, an interferon gamma, is a single-chain polypeptide containing 140 amino acids. Specific effects

of interferon gamma include the enhancement of the oxidative metabolism of macrophages, antibody dependent cellular cytotoxicity, activation of natural killer cells, and the expression of Fc receptors and major histocompatibility antigens.[1]

Disease Overview

Chronic Granulomatous Disease

CGD is an inherited primary immunodeficiency caused by functional impairment of the dihydronicotinamide-adenine dinucleotide phosphate (NADPH) oxidase complex in neutrophilic granulocytes and monocytes characterized by recurrent and severe infections, dysregulated inflammation, and autoimmunity.[2] CGD may present any time from infancy to late adulthood; however, the vast majority of affected individuals are diagnosed before age five years.[3] Some people with chronic granulomatous disease do not have any identified mutation gene. The cause of the condition in these individuals is unknown.[4] Mutations in the CYBA, CYBB, NCF1, NCF2, or NCF4 gene can cause CGD.
The American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI) have jointly accepted responsibility for establishing the practice parameter for the diagnosis and management of primary immunodeficiency.[5] Screening for CGD should include direct measurement of superoxide production (nitroblue tetrazolium reduction test [NBT] or dihydrorhodamine 123 [DHR] oxidation test) confirmed with testing for genetic mutation in the genes that make up the NADPH.[6] Neutrophils from a small sample of peripheral blood are activated to produce superoxide which is detected by the NBT, which is converted from a yellow water-soluble compound to a dark-blue insoluble formazan that can be clearly detected microscopically. Activation of neutrophils with phorbol myristate acetate results in oxidation of DHR to a fluorescent compound, rhodamine 123, which can be measured by flow cytometry. Flow cytometry can distinguish between the different genetic forms of CGD. Summary statement 153 of the practice parameter recommends patients with CGD be given prophylaxis with antimicrobial agents and Actimmune.

Severe, Malignant Osteopetrosis

SMO is an inherited disorder characterized by an osteoclast defect, leading to bone density overgrowth, and by deficient phagocyte oxidative metabolism. This leads to accumulation of bone with defective structure, making them brittle and susceptible to fracture. In some cases, this is also accompanied by skeletal abnormalities.[7] About thirty percent of all cases of osteopetrosis the cause of the condition is unknown, however, nine gene-related mutations are associated with osteopetrosis (CA2, CLCN7, IKBKG, ITGB3, OSTM1, PLEKHM1, TCIRG1, TNFRSF11A, TNFSF11).[8] The Osteopetrosis Working Group developed expert consensus guidelines for the diagnosis and management of osteopetrosis.[9] The guidelines recommend diagnosis is determined by classic radiographic (X-ray) features of osteopetrosis followed up by genetic testing to differentiate between the different forms of osteopetrosis with unique complications. The guidelines suggests the use of Actimmune to be considered experimental in noninfantile osteopetrosis with limited clinical experience. Furthermore, acknowledging the FDA indication for SMO and advising the indication pertains only to severe infantile osteopetrosis.

In both disorders, the exact mechanism(s) of Actimmune's treatment effect has not been established. Changes in superoxide levels during Actimmune therapy do not predict efficacy and should not be used to assess patient response to therapy.[1]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Actimmune. Because of the specialized skills required for evaluation and diagnosis of patients treated with Actimmune as well as the monitoring required for adverse events and long-term efficacy, approval requires Actimmune to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Actimmune is recommended in those who meet the following criteria:

FDA-Approved Indications

116. Chronic Granulomatous Disease. Approve for 1 year if the patient meets of the following criteria (A and B):

A) Diagnosis has been established by a molecular genetic test identifying a gene-related mutation linked to chronic granulomatous disease; AND

Note: Examples of gene-related mutations linked to chronic granulomatous disease include biallelic pathogenic variants in *CYBA*, *CYBB*, *NCF1*, *NCF2*, and *NCF4*.

B) The medication is prescribed by, or in consultation with, an immunologist.

117. Malignant Osteopetrosis, Severe Infantile. Approve for 1 year if the patient meets of the following criteria (A and B):

A) Diagnosis has been established by one of the following (i or ii)

i. Patient has had a radiographic (X-ray) imaging demonstrating skeletal features related to osteopetrosis; OR

ii. Patient has had a molecular genetic test identifying a gene-related mutation linked to malignant osteopetrosis, severe infantile; AND

B) The medication is prescribed by, or in consultation with, an endocrinologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Actimmune has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

118. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/24/2019
Annual revision	**Chronic Granulomatous Disease.** Diagnosis by a dihydrorhodamine flow cytometric test or a nitroblue tetrazolium reduction test was removed from the criteria. Examples of gene-related mutations linked to chronic granulomatous disease were added as a Note.	04/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Iron Replacement – Feraheme Prior Authorization Policy

- Feraheme® (ferumoxytol injection for intravenous use – AMAG Pharmaceuticals)

REVIEW DATE: 12/16/2020

OVERVIEW

Feraheme, an iron replacement product, is indicated for the **treatment of iron deficiency anemia** in patients ≥ 18 years of age for the following uses:[1]

- **Chronic kidney disease** (CKD).
- **Intolerance to oral iron or have had unsatisfactory response to oral iron**.

Guidelines

The KDIGO guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[2] For adults with CKD and anemia not on iron or erythroid stimulating agent (ESA) therapy, a trial of intravenous (IV) iron (or in non-dialysis patients with CKD, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration without starting ESA treatment is desired and transferrin saturation (TSAT) is ≤ 30% and ferritin is ≤ 500 ng/mL. For adults with CKD on ESA therapy who are not receiving iron supplementation, a trial of IV iron (or in non-dialysis CKD patients, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration or a decrease in ESA dose is desired and TSAT is ≤ 30% and ferritin is ≤ 500 ng/mL. For all pediatric patients with CKD with anemia not on iron or ESA therapy, oral iron (or IV iron in patients receiving hemodialysis) is recommended when TSAT is ≤ 20% and ferritin is ≤ 100 ng/mL. For all pediatric patients with CKD who are receiving ESA therapy but not receiving iron supplementation, it is recommended to administer oral iron (or IV iron for patients receiving hemodialysis) to maintain TSAT > 20% and ferritin > 100 ng/dL.

The National Comprehensive Cancer Network guidelines on Hematopoietic Growth Factors (version 2.2020 – January 27, 2020) discuss the management of cancer- and chemotherapy-induced anemia.[3] IV iron therapy is considered an option for patients with absolute iron deficiency (ferritin < 30 ng/mL and TSAT < 20%), functional iron deficiency (ferritin = 30 to 500 ng/mL and TSAT < 50%), and possible functional iron deficiency (ferritin = 501 to 800 ng/mL and TSAT < 50%).

A 2017 focused update of the 2013 American College of Cardiology Foundation/American Heart Association guideline for the management of heart failure.[4] It states that in patients with New York Heart Association class II or III heart failure, absolute iron deficiency (ferritin < 100 ng/mL) or functional iron deficiency (ferritin = 100 to 300 mg/mL if transferring saturation is < 20%), and with or without anemia, IV iron replacement may be reasonable to improve function status and quality of life.[4] Benefits noted with IV iron therapies included improvement in functional capacity, improvements in the six-minute walk test and improved functional capacity.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Feraheme. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Feraheme as well as the monitoring required for adverse events and long-term efficacy, approval requires Feraheme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Feraheme is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis**. Approve for 3 years.

2. **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are not on Dialysis**. Approve for 1 year if the patient meets the following criteria (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Feraheme is prescribed by, or in consultation with a nephrologist or hematologist.

3. **Iron Deficiency Anemia, Other.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient meets one of the following (i, ii, iii, or iv):
      i. Patient meets both of the following (a and b):
         a) Patient has tried oral iron supplementation; AND
         b) According to the prescriber, oral iron supplementation was ineffective or intolerable; OR
      ii. Patient has a condition which, per the prescriber, will interfere with oral iron absorption (e.g., inflammatory bowel disease, Crohn's disease); OR
      iii. Patient is currently receiving an erythroid stimulating agent; OR
      Note: Examples of erythroid stimulating agents include an epoetin alfa product, a darbepoetin alfa product, or a methoxy polyethylene glycol-epoetin beta product.
      iv. The medication is being requested for cancer- or chemotherapy-related anemia.

Other Uses with Supportive Evidence

4. **Iron Deficiency Associated with Heart Failure.** Approve for 1 year if the patient meets the following criteria (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Feraheme is being prescribed by, or in consultation with a cardiologist or hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Feraheme is not recommended in the following situations:

120. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

92. Feraheme® [prescribing information]. Waltham, MA: AMAG Pharmaceuticals; September 2020.
93. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int*. 2012;2(Suppl):279-335.
94. The NCCN® Hematopoietic Growth Factors Guidelines in Oncology (Version 2.2020 – January 27, 2020). 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org/clinical.asp. Accessed on December 1, 2020.
95. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure. *J Am Coll Cardiol*. 2017;70(6):776-803.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/18/2019
Selected Revision	**Iron Deficiency Anemia in Chronic Kidney Disease** was separated into two conditions, **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis** and **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are not on Dialysis.** The indication for **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis** will not be targeted in this policy and all requests are to approve for 3 years.	03/04/2020
Annual Revision	No criteria changes.	12/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Iron Replacement – Ferrlecit Prior Authorization Policy

- Ferrlecit® (sodium ferric gluconate complex in sucrose injection for intravenous use – sanofi-aventis)

REVIEW DATE: 12/16/2020

OVERVIEW

Ferrlecit, an iron replacement product, is indicated for the **treatment of iron deficiency anemia** in patients ≥ 6 years of age with **chronic kidney disease** (CKD) **receiving hemodialysis** who are receiving supplemental epoetin therapy.[1]

Guidelines

The KDIGO guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[2] For adults with CKD and anemia not on iron or erythroid stimulating agent (ESA) therapy, a trial of intravenous (IV) iron (or in non-dialysis patients with CKD, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration without starting ESA treatment is desired and transferrin saturation (TSAT) is ≤ 30% and ferritin is ≤ 500 ng/mL. For adults with CKD on ESA therapy who are not receiving iron supplementation, a trial of IV iron (or in non-dialysis CKD patients, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration or a decrease in ESA dose is desired and TSAT is ≤ 30% and ferritin is ≤ 500 ng/mL. For all pediatric patients with CKD with anemia not on iron or ESA therapy, oral iron (or IV iron in patients receiving hemodialysis) is recommended when TSAT is ≤ 20% and ferritin is ≤ 100 ng/mL. For all pediatric patients with CKD who are receiving ESA therapy but not receiving iron supplementation, it is recommended to administer oral iron (or IV iron for patients receiving hemodialysis) to maintain TSAT > 20% and ferritin > 100 ng/dL.

The National Comprehensive Cancer Network guidelines on Hematopoietic Growth Factors (version 2.2020 – January 27, 2020) discuss the management of cancer- and chemotherapy-induced anemia.[3] IV iron therapy is considered an option for patients with absolute iron deficiency (ferritin < 30 ng/mL and TSAT < 20%), functional iron deficiency (ferritin = 30 to 500 ng/mL and TSAT < 50%), and possible functional iron deficiency (ferritin = 501 to 800 ng/mL and TSAT < 50%).

A 2017 focused update of the 2013 American College of Cardiology Foundation/American Heart Association guideline for the management of heart failure.[4] It states that in patients with New York Heart Association class II or III heart failure, absolute iron deficiency (ferritin < 100 ng/mL) or functional iron deficiency (ferritin = 100 to 300 mg/mL if transferring saturation is < 20%), and with or without anemia, IV iron replacement may be reasonable to improve function status and quality of life.[4] Benefits noted with IV iron therapies included improvement in functional capacity, improvements in the six-minute walk test and improved functional capacity.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ferrlecit. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ferrlecit as well as the monitoring required for adverse events and long-term efficacy, approval requires Ferrlecit to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ferrlecit is recommended in those who meet the following criteria:

FDA-Approved Indications

5. **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis**. Approve for 3 years.

Other Uses with Supportive Evidence

6. **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are not on Dialysis**. Approve for 1 year if the patient meets the following criteria (A and B):
   - **C)** Patient is ≥ 6 years of age; AND
   - **D)** Ferrlecit is prescribed by, or in consultation with a nephrologist or hematologist.

7. **Iron Deficiency Anemia, Other.** Approve for 1 year if the patient meets the following (A and B):
   - **C)** Patient is ≥ 6 years of age; AND
   - **D)** Patient meets one of the following (i, ii, iii, or iv):
     - **i.** Patient meets both of the following (a and b):
       - **a)** Patient has tried oral iron supplementation; AND
       - **b)** According to the prescriber, oral iron supplementation was ineffective or intolerable; OR
     - **ii.** Patient has a condition which, per the prescriber, will interfere with oral iron absorption (e.g., inflammatory bowel disease, Crohn's disease); OR
     - **iii.** Patient is currently receiving an erythroid stimulating agent; OR
       Note: Examples of erythroid stimulating agents include an epoetin alfa product, a darbepoetin alfa product, or a methoxy polyethylene glycol-epoetin beta product.
     - **iv.** The medication is being requested for cancer- or chemotherapy-related anemia.

8. **Iron Deficiency Associated with Heart Failure.** Approve for 1 year if the patient meets the following criteria (A and B):
   - **C)** Patient is ≥ 6 years of age; AND
   - **D)** Ferrlecit is being prescribed by, or in consultation with a cardiologist or hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ferrlecit is not recommended in the following situations:

121. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

96. Ferrlecit® [prescribing information]. Bridgewater, NJ: sanofi-aventis; April 2020.
97. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int*. 2012;2(Suppl):279-335.
98. The NCCN® Hematopoietic Growth Factors Guidelines in Oncology (Version 2.2020 – January 27, 2020). 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org/clinical.asp. Accessed on December 1, 2020.
99. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure. *J Am Coll Cardiol*. 2017;70(6):776-803.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/18/2019
Selected Revision	**Iron Deficiency Anemia in Chronic Kidney Disease** was separated into two conditions, **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis** and **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are not on Dialysis.** The indication for **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis** will not be targeted in this policy and all requests are to approve for 3 years.	03/04/2020
Annual Revision	No criteria changes.	12/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Iron Replacement – INFeD Prior Authorization Policy

- INFeD® (iron dextran injection for intravenous or intramuscular use – Actavis Pharma)

REVIEW DATE: 12/16/2020

OVERVIEW

INFeD, an iron replacement product, is indicated for the treatment of patients with documented **iron deficiency in whom oral administration is unsatisfactory or impossible**.[1]

Guidelines

The KDIGO guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[2] For adults with CKD and anemia not on iron or erythroid stimulating agent (ESA) therapy, a trial of intravenous (IV) iron (or in non-dialysis patients with CKD, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration without starting ESA treatment is desired and transferrin saturation (TSAT) is ≤ 30% and ferritin is ≤ 500 ng/mL. For adults with CKD on ESA therapy who are not receiving iron supplementation, a trial of IV iron (or in non-dialysis CKD patients, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration or a decrease in ESA dose is desired and TSAT is ≤ 30% and ferritin is ≤ 500 ng/mL. For all pediatric patients with CKD with anemia not on iron or ESA therapy, oral iron (or IV iron in patients receiving hemodialysis) is recommended when TSAT is ≤ 20% and ferritin is ≤ 100 ng/mL. For all pediatric patients with CKD who are receiving ESA therapy but not receiving iron supplementation, it is recommended to administer oral iron (or IV iron for patients receiving hemodialysis) to maintain TSAT > 20% and ferritin > 100 ng/dL.

The National Comprehensive Cancer Network guidelines on Hematopoietic Growth Factors (version 2.2020 – January 27, 2020) discuss the management of cancer- and chemotherapy-induced anemia.[3] IV iron therapy is considered an

option for patients with absolute iron deficiency (ferritin < 30 ng/mL and TSAT < 20%), functional iron deficiency (ferritin = 30 to 500 ng/mL and TSAT < 50%), and possible functional iron deficiency (ferritin = 501 to 800 ng/mL and TSAT < 50%).

A 2017 focused update of the 2013 American College of Cardiology Foundation/American Heart Association guideline for the management of heart failure.[4] It states that in patients with New York Heart Association class II or III heart failure, absolute iron deficiency (ferritin < 100 ng/mL) or functional iron deficiency (ferritin = 100 to 300 mg/mL if transferring saturation is < 20%), and with or without anemia, IV iron replacement may be reasonable to improve function status and quality of life.[4] Benefits noted with IV iron therapies included improvement in functional capacity, improvements in the six-minute walk test and improved functional capacity.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of INFeD. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with INFeD as well as the monitoring required for adverse events and long-term efficacy, approval requires INFeD to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of INFeD is recommended in those who meet the following criteria:

FDA-Approved Indications

9. Iron Deficiency Anemia, Other. Approve for 1 year if the patient meets one of the following (A, B, C, or D):
- **E)** Patient meets both of the following (i and ii):
  - **i.** Patient has tried oral iron supplementation; AND
  - **ii.** According to the prescriber, oral iron supplementation was ineffective or intolerable; OR
- **F)** Patient has a condition which, per the prescriber, will interfere with oral iron absorption (e.g., inflammatory bowel disease, Crohn's disease); OR
- **G)** Patient is currently receiving an erythroid stimulating agent; OR
  Note: Examples of erythroid stimulating agents include an epoetin alfa product, a darbepoetin alfa product, or a methoxy polyethylene glycol-epoetin beta product.
- **H)** The medication is being requested for cancer- or chemotherapy-related anemia.

Other Uses with Supportive Evidence

10. Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis. Approve for 3 years.

11. Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are not on Dialysis. Approve for 1 year if the medication is prescribed by, or in consultation with a nephrologist or hematologist.

12. Iron Deficiency Associated with Heart Failure. Approve for 1 year if the medication is being prescribed by, or in consultation with a cardiologist or hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of INFeD is not recommended in the following situations:

122. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

100. INFeD® [prescribing information]. Parsippany, NJ: Actavis Pharma; September 2020.
101. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int*. 2012;2(Suppl):279-335.

102. The NCCN® Hematopoietic Growth Factors Guidelines in Oncology (Version 2.2020 – January 27, 2020). 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org/clinical.asp. Accessed on December 1, 2020.
103. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure. *J Am Coll Cardiol*. 2017;70(6):776-803.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/18/2019
Selected Revision	**Iron Deficiency Anemia in Chronic Kidney Disease** was separated into two conditions, **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis** and **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are not on Dialysis.** The indication for **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis** will not be targeted in this policy and all requests are to approve for 3 years.	03/04/2020
Annual Revision	No criteria changes.	12/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Iron Replacement – Injectafer Prior Authorization Policy

- Injectafer® (ferric carboxymaltose injection for intravenous use – American Regent)

REVIEW DATE: 12/16/2020

OVERVIEW

Injectafer, an iron replacement product, is indicated for the **treatment of iron deficiency anemia** in patients ≥ 18 years of age for the following uses:[1]

- **Intolerance to oral iron or have had unsatisfactory response to oral iron**.
- **Non-dialysis chronic kidney disease** (CKD).

Guidelines

The KDIGO guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[2] For adults with CKD and anemia not on iron or erythroid stimulating agent (ESA) therapy, a trial of intravenous (IV) iron (or in non-dialysis patients with CKD, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration without starting ESA treatment is desired and transferrin saturation (TSAT) is ≤ 30% and ferritin is ≤ 500 ng/mL. For adults with CKD on ESA therapy who are not receiving iron supplementation, a trial of IV iron (or in non-dialysis CKD patients, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration or a decrease in ESA dose is desired and TSAT is ≤ 30% and ferritin is ≤ 500 ng/mL. For all pediatric patients with CKD with anemia not on iron or ESA therapy, oral iron (or IV iron in patients receiving hemodialysis) is recommended when TSAT is ≤ 20% and ferritin is ≤ 100 ng/mL. For all pediatric patients with CKD who are receiving ESA therapy but not receiving iron supplementation, it is recommended to administer oral iron (or IV iron for patients receiving hemodialysis) to maintain TSAT > 20% and ferritin > 100 ng/dL.

The National Comprehensive Cancer Network guidelines on Hematopoietic Growth Factors (version 2.2020 – January 27, 2020) discuss the management of cancer- and chemotherapy-induced anemia.[3] IV iron therapy is considered an option for patients with absolute iron deficiency (ferritin < 30 ng/mL and TSAT < 20%), functional iron deficiency (ferritin = 30 to 500 ng/mL and TSAT < 50%), and possible functional iron deficiency (ferritin = 501 to 800 ng/mL and TSAT < 50%).

A 2017 focused update of the 2013 American College of Cardiology Foundation/American Heart Association guideline for the management of heart failure.[4] It states that in patients with New York Heart Association class II or III heart failure, absolute iron deficiency (ferritin < 100 ng/mL) or functional iron deficiency (ferritin = 100 to 300 mg/mL if transferring saturation is < 20%), and with or without anemia, IV iron replacement may be reasonable to improve function status and quality of life.[4] Benefits noted with IV iron therapies included improvement in functional capacity, improvements in the six-minute walk test and improved functional capacity.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Injectafer. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Injectafer as well as the monitoring required for adverse events and long-term efficacy, approval requires Injectafer to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Injectafer is recommended in those who meet the following criteria:

FDA-Approved Indications

13. **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are not on Dialysis**. Approve for 1 year if the patient meets the following criteria (A and B):
    - **E)** Patient is ≥ 18 years of age; AND
    - **F)** Injectafer is prescribed by, or in consultation with a nephrologist or hematologist.

14. **Iron Deficiency Anemia, Other.** Approve for 1 year if the patient meets the following (A and B):
    - **I)** Patient is ≥ 18 years of age; AND
    - **J)** Patient meets one of the following (i, ii, iii, or iv):
        - **i.** Patient meets both of the following (a and b):
            - **a)** Patient has tried oral iron supplementation; AND
            - **b)** According to the prescriber, oral iron supplementation was ineffective or intolerable; OR
        - **ii.** Patient has a condition which, per the prescriber, will interfere with oral iron absorption (e.g., inflammatory bowel disease, Crohn's disease); OR
        - **iii.** Patient is currently receiving an erythroid stimulating agent; OR
          Note: Examples of erythroid stimulating agents include an epoetin alfa product, a darbepoetin alfa product, or a methoxy polyethylene glycol-epoetin beta product.
        - **iv.** The medication is being requested for cancer- or chemotherapy-related anemia.

Other Uses with Supportive Evidence

15. **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis**. Approve for 3 years.

16. **Iron Deficiency Associated with Heart Failure.** Approve for 1 year if the patient meets the following criteria (A and B):
    - **E)** Patient is ≥ 18 years of age; AND
    - **F)** Injectafer is being prescribed by, or in consultation with a cardiologist or hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Injectafer is not recommended in the following situations:

123. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

104. Injectafer® [prescribing information]. Shirley, NY: American Regent; September 2020.
105. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int*. 2012;2(Suppl):279-335.

106. The NCCN® Hematopoietic Growth Factors Guidelines in Oncology (Version 2.2020 – January 27, 2020). 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org/clinical.asp. Accessed on December 1, 2020.
107. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure. *J Am Coll Cardiol*. 2017;70(6):776-803.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/18/2019
Selected Revision	**Iron Deficiency Anemia in Chronic Kidney Disease** was separated into two conditions, **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis** and **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are not on Dialysis.** The indication for **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis** will not be targeted in this policy and all requests are to approve for 3 years.	03/04/2020
Annual Revision	No criteria changes.	12/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Iron Replacement – Monoferric Prior Authorization Policy

- Monoferric® (ferric derisomaltose injection for intravenous use – Pharmacosmos)

REVIEW DATE: 12/16/2020

OVERVIEW

Feraheme, an iron replacement product, is indicated for the **treatment of iron deficiency anemia** in patients ≥ 18 years of age for the following uses:[1]

- **Chronic kidney disease** (CKD).
- **Intolerance to oral iron or have had unsatisfactory response to oral iron**.

Guidelines

The KDIGO guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[2] For adults with CKD and anemia not on iron or erythroid stimulating agent (ESA) therapy, a trial of intravenous (IV) iron (or in non-dialysis patients with CKD, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration without starting ESA treatment is desired and transferrin saturation (TSAT) is ≤ 30% and ferritin is ≤ 500 ng/mL. For adults with CKD on ESA therapy who are not receiving iron supplementation, a trial of IV iron (or in non-dialysis CKD patients, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration or a decrease in ESA dose is desired and TSAT is ≤ 30% and ferritin is ≤ 500 ng/mL. For all pediatric patients with CKD with anemia not on iron or ESA therapy, oral iron (or IV iron in patients receiving hemodialysis) is recommended when TSAT is ≤ 20% and ferritin is ≤ 100 ng/mL. For all pediatric patients with CKD who are receiving ESA therapy but not receiving iron supplementation, it is recommended to administer oral iron (or IV iron for patients receiving hemodialysis) to maintain TSAT > 20% and ferritin > 100 ng/dL.

The National Comprehensive Cancer Network guidelines on Hematopoietic Growth Factors (version 2.2020 – January 27, 2020) discuss the management of cancer- and chemotherapy-induced anemia.[3] IV iron therapy is considered an option for patients with absolute iron deficiency (ferritin < 30 ng/mL and TSAT < 20%), functional iron deficiency (ferritin = 30 to 500 ng/mL and TSAT < 50%), and possible functional iron deficiency (ferritin = 501 to 800 ng/mL and TSAT < 50%).

A 2017 focused update of the 2013 American College of Cardiology Foundation/American Heart Association guideline for the management of heart failure.[4] It states that in patients with New York Heart Association class II or III heart failure, absolute iron deficiency (ferritin < 100 ng/mL) or functional iron deficiency (ferritin = 100 to 300 mg/mL if transferring saturation is < 20%), and with or without anemia, IV iron replacement may be reasonable to

improve function status and quality of life.[4] Benefits noted with IV iron therapies included improvement in functional capacity, improvements in the six-minute walk test and improved functional capacity.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Monoferric. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Monoferric as well as the monitoring required for adverse events and long-term efficacy, approval requires Monoferric to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Monoferric is recommended in those who meet the following criteria:

FDA-Approved Indications

17. Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are not on Dialysis. Approve for 1 year if the patient meets the following criteria (A and B):
- **G)** Patient is ≥ 18 years of age; AND
- **H)** Monoferric is prescribed by, or in consultation with a nephrologist or hematologist.

18. Iron Deficiency Anemia, Other. Approve for 1 year if the patient meets the following (A and B):
- **K)** Patient is ≥ 18 years of age; AND
- **L)** Patient meets one of the following (i, ii, iii, or iv):
  - **i.** Patient meets both of the following (a and b):
    - **a)** Patient has tried oral iron supplementation; AND
    - **b)** According to the prescriber, oral iron supplementation was ineffective or intolerable; OR
  - **ii.** Patient has a condition which, per the prescriber, will interfere with oral iron absorption (e.g., inflammatory bowel disease, Crohn's disease); OR
  - **iii.** Patient is currently receiving an erythroid stimulating agent; OR
    Note: Examples of erythroid stimulating agents include an epoetin alfa product, a darbepoetin alfa product, or a methoxy polyethylene glycol-epoetin beta product.
  - **iv.** The medication is being requested for cancer- or chemotherapy-related anemia.

Other Uses with Supportive Evidence

19. Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis. Approve for 3 years.

20. Iron Deficiency Associated with Heart Failure. Approve for 1 year if the patient meets the following criteria (A and B):
- **G)** Patient is ≥ 18 years of age; AND
- **H)** Monoferric is being prescribed by, or in consultation with a cardiologist or hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Monoferric is not recommended in the following situations:

124. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

108. Monoferric® injection [prescribing information]. Holbaek, Denmark: Pharmacosmos; January 2020.
109. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int*. 2012;2(Suppl):279-335.

110. The NCCN® Hematopoietic Growth Factors Guidelines in Oncology (Version 2.2020 – January 27, 2020). 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org/clinical.asp. Accessed on December 1, 2020.
111. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure. *J Am Coll Cardiol*. 2017;70(6):776-803.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	03/04/2020
Early Annual Revision	No criteria changes.	12/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Iron Replacement – Venofer Prior Authorization Policy

- Venofer® (iron sucrose injection, for intravenous use – American Regent)

REVIEW DATE: 12/16/2020

OVERVIEW

Venofer, an iron replacement product, is indicated for the treatment of **iron deficiency anemia in patients with chronic kidney disease** (CKD).[1]

Guidelines

The KDIGO guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[2] For adults with CKD and anemia not on iron or erythroid stimulating agent (ESA) therapy, a trial of intravenous (IV) iron (or in non-dialysis patients with CKD, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration without starting ESA treatment is desired and transferrin saturation (TSAT) is ≤ 30% and ferritin is ≤ 500 ng/mL. For adults with CKD on ESA therapy who are not receiving iron supplementation, a trial of IV iron (or in non-dialysis CKD patients, alternatively, a 1 to 3 month trial of oral iron therapy) is recommended if an increase in Hb concentration or a decrease in ESA dose is desired and TSAT is ≤ 30% and ferritin is ≤ 500 ng/mL. For all pediatric patients with CKD with anemia not on iron or ESA therapy, oral iron (or IV iron in patients receiving hemodialysis) is recommended when TSAT is ≤ 20% and ferritin is ≤ 100 ng/mL. For all pediatric patients with CKD who are receiving ESA therapy but not receiving iron supplementation, it is recommended to administer oral iron (or IV iron for patients receiving hemodialysis) to maintain TSAT > 20% and ferritin > 100 ng/dL.

The National Comprehensive Cancer Network guidelines on Hematopoietic Growth Factors (version 2.2020 – January 27, 2020) discuss the management of cancer- and chemotherapy-induced anemia.[3] IV iron therapy is considered an option for patients with absolute iron deficiency (ferritin < 30 ng/mL and TSAT < 20%), functional iron deficiency (ferritin = 30 to 500 ng/mL and TSAT < 50%), and possible functional iron deficiency (ferritin = 501 to 800 ng/mL and TSAT < 50%).

A 2017 focused update of the 2013 American College of Cardiology Foundation/American Heart Association guideline for the management of heart failure.[4] It states that in patients with New York Heart Association class II or III heart failure, absolute iron deficiency (ferritin < 100 ng/mL) or functional iron deficiency (ferritin = 100 to 300 mg/mL if transferring saturation is < 20%), and with or without anemia, IV iron replacement may be reasonable to improve function status and quality of life.[4] Benefits noted with IV iron therapies included improvement in functional capacity, improvements in the six-minute walk test and improved functional capacity.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Venofer. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with

Venofer as well as the monitoring required for adverse events and long-term efficacy, approval requires Venofer to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Venofer is recommended in those who meet the following criteria:

FDA-Approved Indications

21. Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis. Approve for 3 years.

22. Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are not on Dialysis. Approve for 1 year if the medication is prescribed by, or in consultation with a nephrologist or hematologist.

Other Uses with Supportive Evidence

23. Iron Deficiency Anemia, Other. Approve for 1 year if the patient meets one of the following (A, B, C, or D):

M) Patient meets both of the following (i and ii):
- **i.** Patient has tried oral iron supplementation; AND
- **ii.** According to the prescriber, oral iron supplementation was ineffective or intolerable; OR

N) Patient has a condition which, per the prescriber, will interfere with oral iron absorption (e.g., inflammatory bowel disease, Crohn's disease); OR

O) Patient is currently receiving an erythroid stimulating agent; OR
Note: Examples of erythroid stimulating agents include an epoetin alfa product, a darbepoetin alfa product, or a methoxy polyethylene glycol-epoetin beta product.

P) The medication is being requested for cancer- or chemotherapy-related anemia.

24. Iron Deficiency Associated with Heart Failure. Approve for 1 year if the medication is being prescribed by, or in consultation with a cardiologist or hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Venofer is not recommended in the following situations:

125. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/18/2019
Selected Revision	**Iron Deficiency Anemia in Chronic Kidney Disease** was separated into two conditions, **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are on Dialysis** and **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are not on Dialysis.** The indication for **Iron Deficiency Anemia in Patients with Chronic Kidney**	03/04/2020

	Disease who are on Dialysis will not be targeted in this policy and all requests are to approve for 3 years.	
Annual Revision	No criteria changes.	12/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Keveyis Prior Authorization Policy

- Keveyis® (dichlorphenamide tablets – Taro Pharmaceuticals)

REVIEW DATE: 12/02/2020

OVERVIEW

Keveyis, a carbonic anhydrase inhibitor, is indicated for the treatment of **primary hyperkalemic periodic paralysis** (HyperPP), **primary hypokalemic periodic paralysis** (HypoPP), and related variants.[1] These conditions are heterogeneous and response to Keveyis may vary; therefore, prescribers should evaluate the patient's response to Keveyis after 2 months to decide whether it should be continued.

Disease Overview

The primary periodic paralyses are rare muscle disorders caused by autosomal dominant genetic mutations in ion channels.[2,3] The altered channels cannot properly regulate the flow of ions into muscle cells, which reduces the ability of skeletal muscles to contract, leading to severe muscle weakness or paralysis.[4] Genetic testing is recommended as the first diagnostic step; a heterozygous pathogenic mutation can be identified in 60% to 70% of periodic paralysis cases.[5] When a genetic mutation cannot be identified, periodic paralyses can be distinguished based on clinical presentation. Other causes of hypokalemia or hyperkalemia should be excluded.[5]

Regarding treatment, oral potassium salts can be taken as maintenance/prophylactic therapy for patients with HypoPP; however, this does not completely prevent attacks.[6] Although data are limited to case reports and single-blind trials, acetazolamide, another carbonic anhydrase inhibitor, has been used historically for primary periodic paralysis. Acetazolamide treatment is beneficial in approximately 50% of patients with HypoPP and it has no effect in 30% of affected patients. It can also exacerbate symptoms in 20% of patients. Keveyis has been reported to be 30 times more potent than acetazolamide in vitro.[7] Prior to initiating Keveyis it is important to verify if the patient has had exacerbation with acetazolamide, since Keveyis is considered to be more potent and may potentially lead to more exacerbations.[8]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Keveyis. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Keveyis, as well as the monitoring required for adverse events and long-term efficacy, approval requires Keveyis to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Keveyis is recommended in those who meet the following criteria:

FDA-Approved Indications

23. Hypokalemic Periodic Paralysis (HypoPP) and Related Variants. Approve for the duration noted if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve for 2 months if the patient meets the following criteria (i, ii, iii, iv, v, and vi):

i. Patient has a confirmed diagnosis of primary hypokalemic periodic paralysis by meeting at least ONE of the following (a, b, or c):

a) Patient has had a serum potassium concentration of less than 3.5 mEq/L during a paralytic attack; OR

b) Patient has a family history of the condition; OR

c) Patient has a genetically confirmed skeletal muscle calcium or sodium channel mutation; AND

ii. The prescriber has excluded other reasons for acquired hypokalemia (e.g., renal, adrenal, or thyroid dysfunction; renal tubular acidosis; diuretic or laxative abuse); AND

iii. Patient has had improvements in paralysis attack symptoms with potassium intake; AND

iv. Patient has tried oral acetazolamide therapy; AND

v. According to the prescriber, acetazolamide therapy did not worsen the paralytic attack frequency or severity in the patient; AND

vi. The medication is prescribed by or in consultation with a neurologist or a physician who specializes in the care of patients with primary periodic paralysis (e.g., muscle disease specialist, physiatrist).

B) Patient is Currently Receiving Keveyis. Approve for 1 year if the patient has responded to Keveyis (e.g., decrease in the frequency or severity of paralytic attacks) as determined by the prescriber.

24. Hyperkalemic Periodic Paralysis (HyperPP) and Related Variants. Approve for the duration noted if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve for 2 months if the patient meets the following criteria (i, ii, iii, iv and v):

i. Patient has a confirmed diagnosis of primary hyperkalemic periodic paralysis by meeting at least ONE of the following criteria (a, b, c, or d):

a) Patient has had an increase from baseline in serum potassium concentration of greater than or equal to 1.5 mEq/L during a paralytic attack; OR

b) Patient has had a serum potassium concentration during a paralytic attack of greater than 5.0 mEq/L; OR

c) Patient has a family history of the condition; OR

d) Patient has a genetically confirmed skeletal muscle sodium channel mutation; AND

ii. The prescriber has excluded other reasons for acquired hyperkalemia (e.g., drug abuse, renal and adrenal dysfunction); AND

iii. Patient has tried oral acetazolamide therapy; AND

iv. According to the prescriber, acetazolamide therapy did not worsen the paralytic attack frequency or severity in the patient; AND

v. The medication is prescribed by or in consultation with a neurologist or a physician who specializes in the care of patients with primary periodic paralysis (e.g., muscle disease specialist, physiatrist).

B) Patient is Currently Receiving Keveyis. Approve for 1 year if the patient has responded to Keveyis (e.g., decrease in the frequency or severity of paralytic attacks) as determined by the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Keveyis is not recommended in the following situations:

119. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Hypokalemic Periodic Paralysis (HypoPP) and Related Variants:** Criterion added that the prescribing physician has excluded other causes of acquired hypokalemia.	12/19/2018
Annual Revision	"Prescribing physician" updated to "prescriber" throughout criteria.	12/18/2019
Annual Revision	**Hypokalemic Periodic Paralysis (HypoPP) and Related Variants:** Removed examples of oral acetazolamide products from criteria; oral acetazolamide is now only available generically. **Hyperkalemic Periodic Paralysis (HyperPP) and Related Variants:** Removed examples of oral acetazolamide products from criteria; oral acetazolamide is now only available generically.	12/02/2020

PRIOR AUTHORIZATION POLICY

POLICY: Lidocaine Patch Prior Authorization Policy

- Lidoderm® (lidocaine 5% patch – Endo Pharmaceuticals, generics)
- ZTlido™ (lidocaine 1.8% topical system – Scilex)

REVIEW DATE: 08/19/2020

OVERVIEW

Lidocaine 5% patch and ZTlido are indicated for the relief of pain associated with postherpetic neuralgia (PHN).[1,2]

Lidocaine is an amide-type local anesthetic agent whose neuronal membrane stabilizing effect produces a local analgesic effect when applied transdermally.[1,2] The lidocaine penetration into intact skin is adequate to produce an analgesic effect, but less than the amount needed to produce a complete sensory block. In a single-dose, crossover study in healthy volunteers, ZTlido demonstrated equivalent exposure and peak concentration of lidocaine to lidocaine patch 5% (Lidoderm, generics).[2]

Other Uses with Supportive Evidence

Lidocaine 5% patches have been shown to be effective in treating low back pain in open-label studies in patients not achieving adequate pain relief despite as needed or stable doses of non-selective nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, gabapentin, tramadol, or opioids.[3-5] The guidelines for treatment of low back pain (2017) do not address the use of topical lidocaine; however, various other agents are used for pain associated with low back pain.[6] In patients with acute or subacute low back pain, the guidelines recommend NSAIDs or skeletal muscle relaxants as pharmacologic treatment options (strong recommendation; moderate-quality evidence). In patients with chronic low back pain who have had an inadequate response to nonpharmacologic therapy, the guidelines recommend consideration of pharmacologic treatment with NSAIDs as first-line therapy or tramadol or duloxetine as second-line therapy. Of note, tramadol is a narcotic and, like other opioids, is associated with the risk for abuse. Clinicians should only consider opioids as an option in patients who have failed the aforementioned treatments and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients (weak recommendation; moderate-quality evidence). Moderate-quality evidence showed no difference in pain between tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs) vs. placebo, and low-quality evidence showed no differences in function for antidepressants. Moderate-quality evidence showed that duloxetine was associated with a small improvement in pain intensity and function vs. placebo.

Lidocaine 5% patch has been shown to be effective in treating neuropathic pain of various forms and etiologies as monotherapy and, more commonly, as adjunctive therapy to a stable analgesic regimen.[3,7-14] There is evidence to suggest that lidocaine 5% patch, along with several other analgesics (i.e., opioids, tramadol, TCAs), can be effective as first-line therapy in the management of neuropathic pain.[12] The 2011 evidence-based guideline on treatment of painful diabetic neuropathy, published by the American Academy of Neurology (AAN), indicates the lidocaine 5% patch may be considered for the treatment of painful diabetic neuropathy.[15] Recommendations for the pharmacological management of neuropathic pain, published by the Mayo Foundation, indicate that lidocaine 5% patch has shown efficacy in patients with varying types of neuropathic pain, and are considered a first-line therapy.[16]

Several open-label trials have shown lidocaine 5% patches to be effective in treating pain associated with osteoarthritis of the knee both as monotherapy and in combination with other analgesics (e.g., NSAIDs, COX-2 inhibitors, opioids, tramadol, acetaminophen).[17-20] In one open-label comparative trial (prematurely terminated before enrollment goals were achieved due to safety concerns surrounding the entire COX-2 class),[21] treatment of knee osteoarthritis with lidocaine 5% patches (1 ⅓ patches applied every 24 hours) resulted in comparable reductions in pain intensity scores as celecoxib 200 mg/day.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of lidocaine patches. All approvals are provided for the duration noted below.

Automation: When available, the ICD-10 codes for postherpetic polyneuropathy (B02.23) will be used as part of automation to allow approval of the requested medication.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of lidocaine patches is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Postherpetic Neuralgia (PHN).** Approve for 3 years.

Other Uses with Supportive Evidence

2. **Low Back Pain.** Approve for 3 years after trying at least three pharmacologic therapies with each one from a different class of medication used to treat low back pain.
   Note: Examples of different classes of pharmacologic therapies for low back pain include acetaminophen, nonsteroidal anti-inflammatory drugs, muscle relaxants, celecoxib, duloxetine, gabapentin. Examples of nonsteroidal anti-inflammatory drugs include etodolac, meloxicam, and nabumetone. Examples of muscle relaxants include carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, and orphenadrine.

3. **Neuropathic Pain.** Approve for 3 years.
   Note: For neuropathic pain due to radiculopathy or sciatica, please refer to the Not Recommended for Approval section for Radiculopathy or Sciatica.

4. **Osteoarthritis.** Approve for 3 years after trying at least three pharmacologic therapies with each one from a different class of medication used for the treatment of osteoarthritis.
   Note: Examples of different classes of pharmacologic therapies for osteoarthritis include acetaminophen, celecoxib, nonsteroidal anti-inflammatory drugs, salicylates, intraarticular glucocorticoids, intraarticular hyaluronan, topical capsaicin, and topical methylsalicylate.[22] Examples of nonsteroidal anti-inflammatory drugs include etodolac, meloxicam, and nabumetone.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of lidocaine patches is not recommended in the following situations:

120. **Carpal Tunnel Syndrome.** Two open-label trials have investigated the lidocaine 5% patch for the relief of pain associated with carpal tunnel symdrome.[23,24] In an open-label, parallel-group, single-center, active-controlled trial,[23] 40 patients with carpal tunnel syndrome were randomized to daily treatment with lidocaine patch 5% or an injection of lidocaine 1% plus methylprednisolone. After 4 weeks of treatment, both groups reported statistically significant improvement in pain scores. A 6-week, randomized, parallel-group, open-label multicenter study[24] found that lidocaine 5% patches given every 24 hours and naproxen 500 mg twice daily both led to significant reductions is the Average Pain Intensity scores in 100 patients with carpal tunnel syndrome. The 2016 American Academy of Orthopaedic Surgeons (AAOS) guidelines on carpal tunnel syndrome do not mention topical lidocaine in their recommendations for treatment.[25] In addition, the AAOS guidelines have a supplemental evidence table that addresses the studies AAOS evaluated for their guidelines. This table states that the above-referenced articles were excluded from their guidelines because they used non-validated outcome measures.

121. **Fibromyalgia.** There are no data available on the use of lidocaine patches in treating pain associated with fibromyalgia.

122. **Myofascial Pain as Adjunctive Therapy.** Published data are limited to small ($n \leq 60$ in each study) studies of lidocaine 5% patches.[26-29] Larger, controlled studies are needed to fully determine the place in therapy of lidocaine patches for the treatment of myofascial pain.

123. **Pain Associated with Rib Fractures.** Lidocaine 5% patch did not significantly improve pain control in patients with traumatic rib fractures in one randomized, double-blind, placebo-controlled study.[30] A retrospective chart analysis found lidocaine patches decreased pain scores in 29 patients with rib

fractures vs. 29 matched controls, with no change in narcotic use and no difference in time to return to baseline activity.[31] A small (n = 44) double-blind, placebo-controlled study in hospitalized patients with traumatic rib fracture in Taiwan found that lidocaine 5% patch decreased pain scores after Day 5 of therapy vs. placebo, with no difference in oral opioid use but decreased meperidine injection use.[32] Larger, controlled studies are needed to fully determine the place in therapy of lidocaine 5% patch for the treatment of pain associated with rib fractures.

124. Radiculopathy. Published data on the use of lidocaine patches in treating pain associated with radiculopathy is limited.[11,33] Larger, controlled studies are needed to fully determine the place in therapy of lidocaine patches for the treatment of radiculopathy.

125. Rheumatoid Arthritis (RA). There are no data available on the use of lidocaine patches in treating pain associated with RA.

126. Sciatica. There are no data available on the use of lidocaine patches in treating pain associated with sciatica.

127. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No change to criteria.	08/01/2018
Selected Revision	Addition of ZTlido to policy. No change to criteria.	10/3/2018
Annual Revision	For the Other Use with Supportive Evidence of Osteoarthritis, the words "of the hand, hip, or knee" were removed from the requirement to try at least three pharmacologic therapies with each one from a different class of medication used for the treatment of osteoarthritis of the hand, hip, and knee. Radiculopathy was added to the policy as a Condition Not Recommended for Approval.	08/07/2019
Annual Revision	No change to criteria. ICD-9 codes were removed from the Automation section because they are no longer used. For the approval conditions of Low Back Pain and Osteoarthritis, examples of different classes of pharmacologic therapies were moved to notes.	08/19/2020

PRIOR AUTHORIZATION POLICY

POLICY: Lipodystrophy – Egrifta® (tesamorelin injection – EMD Serono)

DATE REVIEWED: 04/15/2020

OVERVIEW

Egrifta is an analog of human growth hormone-releasing factor (GRF), indicated for the reduction of excess abdominal fat in human immunodeficiency virus (HIV)-infected patients with lipodystrophy.[1-3] At this time, the long-term cardiovascular (CV) safety and potential long-term CV benefit are not established and careful consideration should be given to continue Egrifta in patients who do not show a clear efficacy response, as judged by the degree of reduction in visceral adipose tissue.[1] Egrifta has a weight-neutral effect and is not indicated for weight loss management. There are no data supporting improved compliance with anti-retroviral therapies in HIV-positive patients who take Egrifta. In the pivotal trial, all patients had lipodystrophy and excess abdominal fat, evidenced by a waist circumference ≥ 95 cm (≥ 94 cm for women) and a waist-to-hip ratio ≥ 0.94 (≥ 0.88 for women). Patients were required to be on a stable antiretroviral regimen for at least 8 weeks. Safety and effectiveness of Egrifta have been established in patients between the ages of 18 and 65 years of age.

Disease Overview

Lipodystrophy is the change in body fat which affects some patients with HIV infection, either due HIV infection or due to medication to treat HIV.[5] Egrifta binds and stimulates human GRF receptors with similar potency as endogenous GRF. GRF stimulates the synthesis and pulsatile release of endogenous growth hormone (GH), which is both anabolic and lipolytic. GH exerts its effect by interacting with receptors on a variety of target cells resulting in the pharmacodynamic effect. A decrease in nocturnal secretion of GH and insulin-like growth factor 1 (IGF-1) is associated with increased visceral adipose tissue (VAT) in patients with HIV-associated lipodystrophy.[2] Egrifta increases secretion of GH and has been shown to decrease VAT and spare subcutaneous adipose tissue (SAT).[3-4] Egrifta is contraindicated in patients with disruption of the hypothalamic-pituitary axis due to hypophysectomy, hypopituitarism, pituitary tumor or surgery, head irradiation, or head trauma; patients with known hypersensitivity to Egrifta or mannitol; pregnant women; and in patients with an active malignancy.[1] Any pre-existing malignancy should be inactive; patients should complete treatment prior to beginning Egrifta.

Other Therapies

There are no other therapies approved specifically for treatment of HIV-associated lipodystrophy and treatment options are limited.[5-6] Administration of GH has demonstrated a significant decrease in VAT, but also a decrease in SAT, compared with placebo.[7] Management strategies for lipodystrophy include: switching antiretroviral therapy, exercise and diet, cosmetic procedures (e.g., liposuction, facial fillers), and prevention of lipodystrophy by selection of regimens less likely to cause lipohypertrophy.[6]

Safety

Because the long-term CV safety and potential long-term CV benefit are not established, careful consideration should be given whether to continue Egrifta treatment in patients who do not show a clear efficacy response, as judged by the degree of reduction in visceral adipose tissue measured by waist circumference or CT scan. In the pivotal studies, efficacy of Egrifta was assessed at Week 26. Because Egrifta induces the release of endogenous GH (a known growth factor) and increases serum IGF-1, the benefits of treatment should be weighed against the increased risk of malignancies in HIV-positive patients. Since the effect of prolonged IGF-1 elevations on the development or progression of malignancies is unknown, monitor IGF-1 levels closely during Egrifta therapy and consider discontinuation in patients with persistent elevations of IGF-1 levels (e.g., > 3 standard deviation scores [SDS]), especially if the patient has not experienced a robust response. Egrifta should be used with caution in patients who develop glucose intolerance or diabetes; discontinuation of therapy should be considered for patients who do not show a clear efficacy response.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Egrifta. Because of the specialized skills required for evaluation and diagnosis of patients treated with Egrifta as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Egrifta to be prescribed by or in consultation with a physician who specializes in the condition being treated. In the approval indication, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression. When approvals are authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Egrifta is recommended in those who meet the following criteria:

FDA-Approved Indications

C) Lipodystrophy in Human Immunodeficiency Virus (HIV)-Infected Patients. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following criteria (i, ii, iii, iv, and v):

ii. The patient is ≥ 18 years of age; AND

iii. Egrifta is prescribed for the reduction of excess abdominal fat; AND

iv. The patient meets ONE of the following (1 or 2):

a) If male*, waist circumference is ≥ 95 cm (37.4 in) and waist-to-hip ratio is ≥ 0.94; OR

b) If female*, waist circumference is ≥ 94 cm (37 in) and waist-to-hip ratio is ≥ 0.88; AND

v. The patient has been stable on an anti-retroviral regimen for at least 8 weeks.
Note: Examples include antiretroviral regimens containing protease inhibitors, nucleoside reverse-transcriptase inhibitors, and/or nonnucleoside reverse-transcriptase inhibitors; AND

vi. Egrifta is prescribed by or in consultation with an endocrinologist or a physician specializing in the treatment of human immunodeficiency virus (HIV) infection (e.g., infectious disease [ID], oncology).

B) Patient is Currently Receiving Egrifta. Approve for 1 year if the patient has responded, as determined by the prescriber.
Note: Examples of a response include reduction in visceral adipose tissue measured by waist circumference or computed tomography (CT) scan.

***** Refer to the Policy Statement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Egrifta has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

128. Abdominal Obesity in Patients without Human Immunodeficiency Virus (HIV) Infection. More data are needed. Egrifta has been studied in a very limited number patients who have abdominal obesity without HIV infection.[8] To be eligible for the published trial, patients were required to have a peak stimulated GH no higher than 9 µg/L on a standardized GH-releasing hormone (GHRH)-arginine stimulation test. Patients (n = 60) were randomized in a 1:1 ratio to treatment with Egrifta 2 mg once

daily (QD) or placebo. The primary endpoint was the change in VAT from baseline. Over 12 months (using last observation carried forward [LOCF]), VAT improved significantly in patients treated with Egrifta compared with placebo (net treatment effect vs. placebo: -35 [95% confidence interval {CI}: -58, -12]; P = 0.003). Treatment with Egrifta increased IGF-1 by 90%, decreased triglycerides by 20%, and decreased log C-reactive protein (CRP) by 24% compared with placebo. There was no effect on total cholesterol, high-density lipoprotein cholesterol (HDL-C), or low-density lipoprotein cholesterol (LDL-C) in the treatment groups.

129. **Human Immunodeficiency Virus (HIV)-Related Cachexia, Weight Loss, or Fat Distribution other than Lipodystrophy.** Egrifta has not been studied in these conditions.

130. **Patients > 65 Years of Age.** There is no information on the use of Egrifta in patients greater than 65 years of age with HIV and lipodystrophy.[1]

131. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual revision	No criteria changes.	03/08/2017
Annual revision	No criteria changes.	04/04/2018
Annual revision	No criteria changes.	04/10/2019
Annual revision	**Lipodystrophy in Human Immunodeficiency Virus (HIV)-Infected Patients:** Add a criterion that requires patients initiating therapy to be stable on an antiretroviral regimen for	04/15/2020

	at least 8 weeks. For initial therapy, criteria were added to require the patient has lipodystrophy and excess abdominal fat, as evidenced by waist circumference (≥ 95 cm for men and ≥9 4 cm for women) and waist-to-hip ratio (≥ 0.94 for men and ≥ 0.88 for women). For patients continuing therapy, the approval duration was changed to be 1 year (previously was 3 years). Examples of a response to therapy were moved to a Note in the criteria. **Conditions Not Recommended for Coverage:** Patients > 65 Years of Age were added to this section of the policy.	
Update	**04/16/2020:** The following was added to the Policy Statement: In the approval indication, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.	--

PRIOR AUTHORIZATION POLICY

POLICY: Lipodystrophy – Myalept Prior Authorization Policy

- Myalept® (metreleptin for subcutaneous injection – Aegerion)

REVIEW DATE: 10/21/2020

OVERVIEW

Myalept, a recombinant analog of human leptin, is indicated as an adjunct to diet as replacement therapy to treat complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy.[1] Limitations of Use: The safety and efficacy of Myalept have not been established for the treatment of complications of partial lipodystrophy, liver disease (including nonalcoholic steatophepatitis [NASH], human immunodeficiency virus (HIV)-related lipodystrophy, or metabolic disease (including diabetes mellitus and hypertriglyceridemia) without concurrent evidence of generalized lipodystrophy.

Disease Overview

Generalized lipodystrophy is a rare, "ultra-orphan", chronic, heterogeneous, and life-threatening disorder in which there is an abnormality of adipose tissue distribution and insufficient fat tissue, which is required for normal metabolic function.[2] Robust epidemiological data are not available. Approximately 400 cases of generalized lipodystrophy have been reported in the literature.[2,3] A recent publication estimates the prevalence of all types of lipodystrophy to be between 1.3 and 4.7 cases per million based on available literature, with the prevalence of generalized lipodystrophy estimated to be much lower at approximately 0.23 cases per million.[24] Although there is heterogeneity in the lipodystrophy syndromes, all share the feature of subcutaneous (SC) adipose tissue loss resulting in more severe metabolic abnormalities (e.g., diabetes mellitus and hypertriglyceridemia) than generally noted with obesity.[4-5]

Guidelines

Guidelines on the diagnosis and management of lipodystrophy syndromes were published in 2016 and endorsed by multiple groups of endocrine experts, including the Endocrine Society, the Pediatric Endocrine Society, the American Diabetes Association, and the American Association of Clinical Endocrinologists.[7] These guidelines note that lipodystrophy is an incurable condition and no treatment will regrow adipose tissue. Myalept is the only drug specifically indicated for the treatment of lipodystrophy. Myalept, along with diet, is recommended as the first-line treatment for metabolic and endocrine abnormalities in patients with generalized lipodystrophy (Class I, Level B). In children, Myalept may also be used to prevent the development of comorbidities (Class IIb, Level C). While not FDA-approved for use in patients with partial lipodystrophy, the guidelines state that Myalept may be used in this setting, if the patient is hypoleptinemic (leptin < 4 ng/mL) and has a glycosylated hemoglobin (HbA1c) > 8% and/or triglycerides > 500 mg/dL (Class IIb, Level B); although it is noted that response to.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Myalept. Because of the specialized skills required for evaluation and diagnosis of patients treated with Myalept, as well as the monitoring required for adverse events and long-term efficacy, approval requires Myalept to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Myalept is recommended in those who meet the following criteria:

FDA-Approved Indication

25. Generalized Lipodystrophy (Congenital or Acquired): Approve for 3 years if the medication is prescribed by, or in consultation with, an endocrinologist or a geneticist physician specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Myalept is not recommended in the following situations:

132. General Obesity not associated with Congenital Leptin Deficiency. Myalept is contraindicated in patients with general obesity not associated with congenital leptin deficiency.[1] Myalept was previously evaluated in two clinical development programs for obesity, both as monotherapy (n > 1,100) and in combination with Symlin® (pramlintide acetate for injection; n > 600).[4] Published studies on the effects of leptin therapy in these patients without leptin deficiency yielded conflicting efficacy results.[8-9] The studies involving obese patients (some with type 2 diabetes mellitus), with the exception of one dose-escalation trial, failed to show significant weight loss with Myalept therapy and resulted in clinically insignificant changes in other metabolic parameters, such as insulin sensitivity.[10-14] One additional randomized, double-blind, placebo-controlled crossover study evaluated the efficacy of leptin administration to promote further weight reduction in patients who had undergone Roux-en-Y gastric bypass surgery.[20] Following 16 weeks of therapy, Myalept was not found to promote additional decreases in body weight compared with placebo.

133. Human Immunodeficiency Virus (HIV)-related Lipodystrophy. Myalept is not indicated for the treatment of patients with HIV-related lipodystrophy.[1] Results from four small studies of patients with HIV-associated lipodystrophy and leptin deficiency showed mixed results with Myalept therapy.[15-18] One study found significantly improved fasting insulin levels, insulin resistance and high-density lipoprotein (HDL) levels, but no significant differences in fasting glucose levels, free-fatty acid levels, or low-density lipoprotein (LDL) levels when Myalept was compared with placebo.[15] Another demonstrated improved fasting insulin levels, but no difference in intravenous glucose disappearance, fasting serum glucose concentration, glycosylated hemoglobin (HbA_{1C}) levels, body mass index (BMI), or lipid parameters after treatment with Myalept.[16] Two additional studies found that therapy with Myalept improved some, but not all metabolic parameters in patients infected with HIV.[17,18] More information is needed to determine if Myalept is a safe and effective treatment for HIV-related lipodystrophy.

134. Partial Lipodystrophy. The safety and efficacy of Myalept in the treatment of the complications of partial lipodystrophy have not been established.[1] The effects of Myalept therapy in patients with partial lipodystrophy have been evaluated; the pivotal trial of Myalept included a subset of patients (n

= 24) with partial lipodystrophy.[19] Overall, patients with partial lipodystrophy had milder baseline metabolic abnormalities than patients with generalized lipodystrophy. Following 12 months of Myalept therapy, patients experienced a reduction in HbA_{1C}, fasting plasma glucose, and fasting triglycerides; however, the magnitude of the improvements was less than those observed in patients with generalized lipodystrophy. There are data showing sustained improvements out to 36 months as well.[25] Additional data also highlight the heterogeneity of partial lipodystrophy; Myalept may provide improvement in some metabolic parameters in certain patients with partial lipodystrophy, but more data are needed to confirm these benefits.[21-23] Current lipodystrophy guidelines (2016) outline certain patients with partial lipodystrophy that may benefit from Myalept therapy, but indicate a lower level of evidence to support use in this patient population compared with generalized lipodystrophy.[7] Myalept prescribing information continues to list partial lipodystrophy as a limitation of use.[1]

135. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	09/12/2018
Annual Revision	No criteria changes.	09/25/2019
Annual Revision	No criteria changes.	10/21/2020

PRIOR AUTHORIZATION POLICY

POLICY: Lucemyra Prior Authorization Policy

- Lycemyra™ (lofexidine tablets – US WorldMeds)

REVIEW DATE: 07/22/2020

OVERVIEW

Lucemyra, a central alpha-2 adrenergic agonist, is indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults.[1] The usual Lucemyra starting dosage is 0.54 mg (three 0.18 mg tablets) four times daily (QID) during the period of peak withdrawal symptoms (generally the first 5 to 7 days following last use of opioid) with dosing guided by symptoms and adverse events. There should be 5 to 6 hours between each dose. The total daily dosage of Lucemyra should not exceed 2.88 mg (16 tablets), and no single dose should exceed 0.72 mg (four tablets). Lucemyra treatment may continue for up to 14 days with dosing guided by symptoms. Discontinue Lucemyra with a gradual dose reduction over a 2- to 4-day period to mitigate Lucemyra withdrawal symptoms (e.g., reducing by one tablet per dose every 1 to 2 days). The Lucemyra dose should be reduced, held, or discontinued for individuals who demonstrate a greater sensitivity to Lucemyra adverse events. Lower doses may be appropriate as opioid withdrawal symptoms wane. Lucemyra can be administered in the presence or absence of food. Dosage adjustments are recommended for patients with hepatic or renal impairment. In the pivotal trials for Lucemyra, patients also had access to a variety of support medications for withdrawal symptoms (e.g., guaifenesin, antacids, docusate sodium, psyllium, bismuth sulfate, acetaminophen, and zolpidem).

Clonidine is not approved by the FDA for use in opioid withdrawal but it has been extensively studied and used for this indication outside the US.[2,3] Clonidine reduces withdrawal symptoms such as nausea, vomiting, diarrhea, cramps, and sweating. Doses of 0.1 mg to 0.3 mg every 6 to 8 hours, to a maximum dose of 1.2 mg/day, may be used to assist in the management of opioid withdrawal symptoms. As with Lucemyra, clonidine can be combined with other non-narcotic medications targeting specific opioid

withdrawal symptoms such as benzodiazepines for anxiety, loperamide for diarrhea, acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) for pain, and ondansetron or other agents for nausea.

Disease Overview

Opioid addiction (or opioid use disorder) is a primary, chronic and relapsing central nervous system (CNS) disease of brain reward, motivation, memory, and related circuitry characterized by an individual pathologically pursuing reward and/or relief by substance use and other behaviors.[4] Since the 1990s, opioid use and abuse have risen markedly in the US.[5] Symptoms of opioid withdrawal include the following: autonomic (diarrhea, rhinorrhea, diaphoresis, lacrimation, shivering, nausea, emesis, piloerection); CNS arousal (sleeplessness, restlessness, tremors); pain (abdominal cramping, bone pains, diffuse muscle aching); and craving for the opioid medication. Symptoms of opioid withdrawal usually begin two to three half-lives after the last opioid dose (6 to 12 hours for short half-life opioids such as heroin and morphine and 36 to 48 hours for long half-life opioids such as methadone).[6] Following cessation of a short half-life opioid, symptoms reach peak intensity within 2 to 4 days, with most of the physical withdrawal signs no longer apparent after 7 to 14 days. As with the onset of withdrawal, the duration also varies with the half-life of the opioid used and the duration of use. While opioid withdrawal is rarely life-threatening, the combination of uncomfortable symptoms and intense craving makes completion of withdrawal difficult for most people.

Guidelines

The American Psychiatric Association (APA) practice guideline for the treatment of patients with substance use disorders (2006) notes several strategies as effective treatments for opioid dependence including the abrupt discontinuation of the opioid with the use of clonidine to suppress withdrawal symptoms and clonidine-naltrexone detoxification, where withdrawal symptoms are precipitated by naltrexone and then suppressed by clonidine.[2] The guidelines note that the completion rate for clonidine-treated outpatients is relatively low and roughly comparable to that of methadone withdrawal.

The American Society of Addiction Medicine (ASAM) practice guideline for the treatment of opioid use disorder (2020) discusses two primary strategies for the management of opioid withdrawal.[3] In one strategy, alpha-2 adrenergic agonists (i.e., clonidine, Lucemyra) are used along with other non-narcotic medications to reduce withdrawal symptoms. The use of non-opioid medications may be the only option available in some healthcare settings and may also assist the transition of patients to opioid antagonist medications (i.e., naltrexone) helping to prevent subsequent relapse. Comparative data are limited but Lucemyra and clonidine appear to be similarly effective in the treatment of opioid withdrawal with hypotension occurring less frequently with Lucemyra. While clonidine is not FDA-approved for the treatment of opioid withdrawal, it has been extensively used off-label for this purpose. Clonidine can be combined with other non-narcotic medications targeting specific opioid withdrawal symptoms. ASAM states that alpha-2 adrenergic agonists are safe and effective for management of opioid withdrawal. However, the guideline notes that methadone and buprenorphine are more effective in reducing the symptoms of opioid withdrawal, in retaining patients in withdrawal management, and in supporting the completion of withdrawal management.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Lucemyra. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lucemyra as well as the monitoring required for adverse events, initial approval requires Lucemyra to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lucemyra is recommended in those who meet the following criteria:

FDA-Approved Indications

26. Opioid Withdrawal Symptoms. Approve for 2 weeks (14 days) if the patient meets the following criteria (A and B):
- **77.** Lucemyra is being used to facilitate abrupt opioid discontinuation; AND
- **78.** Patient has a history of clonidine use (e.g., patches, tablets) and experienced unacceptable toxicity and/or inadequate efficacy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lucemyra is not recommended in the following situations:

136. Cannabis Use Disorder (Cannabis Dependence). One published study has evaluated the safety and efficacy of dronabinol and lofexidine in treating cannabis dependence (n = 156).[7] In this 11-week, placebo-controlled study, the combined intervention did not show efficacy as a treatment for cannabis use disorder.

137. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/25/2018
Annual revision	No changes to criteria.	07/31/2019
Annual revision	No changes to criteria.	07/22/2020

PRIOR AUTHORIZATION POLICY

POLICY: Lupus – Benlysta Prior Authorization Policy

- Benlysta® (belimumab intravenous injection – Human Genome Sciences/GlaxoSmithKline)

REVIEW DATE: 01/20/2021

OVERVIEW

Benlysta intravenous, a B-lymphocyte stimulator (BLyS)-specific inhibitor, is indicated for the following uses:[1]

- **Lupus nephritis**, in adults with active disease who are receiving standard therapy.
- **Systemic lupus erythematosus** (SLE), in patients ≥ 5 years of age with active, autoantibody-positive, systemic disease in those who are receiving standard therapy.

Benlysta intravenous has not been studied and is not recommended in those with severe active central nervous system lupus, or in combination with other biologics. In some of the clinical trials involving Benlysta, Black patients had a lower response rate for the primary endpoint relative to Black patients receiving placebo; therefore, caution is recommended when considering Benlysta in Black patients. Of note, there is also a subcutaneous formulation of Benlysta with a similar indication except use is limited to adults ≥ 18 years.

Guidelines

Benlysta is addressed in the following guidelines:

- **Lupus Nephritis:** Guidelines for lupus nephritis are available from the European League Against Rheumatism (EULAR) and European Renal Association/European Dialysis and Transplant Association (ERA-EDTA) [2019].[3] Benlysta may be considered as add-on treatment for non-responding/refractory lupus nephritis, to facilitate glucocorticoid sparing, control extra-renal lupus activity, and decrease the risk for extra-renal flares.
- **SLE:** Guidelines from the EULAR (2019) recommend consideration of add-on therapy with Benlysta for patients who have an inadequate response to standard of care (e.g., combinations of hydroxychloroquine and glucocorticoids with or without immunosuppressive agents).[2] EULAR defines an inadequate response as residual disease activity not allowing tapering of glucocorticoids and/or frequent relapses.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Benlysta intravenous. Approvals are authorized for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Benlysta intravenous as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Benlysta intravenous to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Benlysta IV is recommended in those who meet the following criteria:

FDA-Approved Indications

D) Lupus Nephritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

1. Initial Therapy. Approve for 6 months if the patient meets ALL of the following conditions (i, ii, iii, and iv):

a. Patient is ≥ 18 years of age; AND

b. Patient has autoantibody-positive SLE, defined as positive for antinuclear antibodies (ANA) and/or anti-double-stranded DNA (anti-dsDNA) antibody; AND

c. Patient meets ONE of the following (a or b):

a) The medication is being used concurrently with at least one other standard therapy; OR
Note: Examples of standard therapies include azathioprine, mycophenolate mofetil, cyclophosphamide.

b) Patient is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber; AND

ii. The medication is prescribed by or in consultation with a nephrologist or rheumatologist.

B) Patient is Currently Receiving Benlysta Intravenous or Subcutaneous. Approve for 1 year if the patient meets ALL of the following criteria (i, ii, and iii):

i. Patient meets ONE of the following (a or b):

a) The medication is being used concurrently with at least one other standard therapy; OR
Note: Examples of standard therapies include azathioprine, mycophenolate mofetil, cyclophosphamide.

b) Patient is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber; AND

ii. The medication is prescribed by or in consultation with a nephrologist or rheumatologist.; AND

iii. Patient has responded to Benlysta subcutaneous or intravenous, as determined by the prescriber.
Note: Examples of a response include improvement in organ dysfunction, reduction in flares, reduction in corticosteroid dose, decrease of anti-dsDNA titer, and improvement in complement levels (i.e., C3, C4).

2. Systemic Lupus Erythematosus. Approve for the duration noted if the patient meets ONE of the following (A or B):

E) Initial Therapy. Approve for 4 months if the patient meets ALL of the following conditions (i, ii, iii, and iv):

i. Patient is ≥ 5 years of age; AND

ii. Patient has autoantibody-positive SLE, defined as positive for antinuclear antibodies (ANA) and/or anti-double-stranded DNA (anti-dsDNA) antibody; AND
Note: Not all patients with SLE are positive for anti-dsDNA, but most will be positive for ANA.

iii. Patient meets ONE of the following (a or b):

a) The medication is being used concurrently with at least one other standard therapy; OR
Note: Examples of standard therapies include an antimalarial (e.g., hydroxychloroquine), systemic corticosteroid (e.g., prednisone), and other immunosuppressants (e.g., azathioprine, mycophenolate mofetil, methotrexate).

b) Patient is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber; AND

iv. The medication is prescribed by or in consultation with a rheumatologist, clinical immunologist, nephrologist, neurologist, or dermatologist.

B) Patient is Currently Receiving Benlysta Intravenous or Subcutaneous. Approve for 1 year if the patient meets ALL of the following criteria (i, ii, and iii):

i. Patient meets ONE of the following (a or b):

a) The medication is being used concurrently with at least one other standard therapy; OR

Note: Examples of standard therapies include an antimalarial (e.g., hydroxychloroquine), systemic corticosteroid (e.g., prednisone), and other immunosuppressants (e.g., azathioprine, mycophenolate mofetil, methotrexate).

b) Patient is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber; AND

ii. The medication is prescribed by or in consultation with a rheumatologist, clinical immunologist, nephrologist, neurologist, or dermatologist; AND

iii. Patient has responded to Benlysta subcutaneous or intravenous, as determined by the prescriber.

Note: Examples of a response include reduction in flares, reduction in corticosteroid dose, decrease of anti-dsDNA titer, improvement in complement levels (i.e., C3, C4), or improvement in specific organ dysfunction (e.g., musculoskeletal, blood, hematologic, vascular, others).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Benlysta Intravenous is not recommended in the following situations:

1. **Concurrent Use with Other Biologics.** Benlysta intravenous has not been studied and is not recommended in combination with other biologics.[1] Safety and efficacy have not been established with these combinations. See APPENDIX for examples of other biologics that should not be taken in combination with Benlysta.

2. **Rheumatoid Arthritis.** A Phase II dose-ranging study evaluating patients with rheumatoid arthritis showed only small American College of Rheumatology 20 responses with Benlysta (e.g., American College of Rheumatology [ACR] 20 response at Week 24 was 28% with Benlysta 10 mg/kg).[4] Numerous other agents are available with higher ACR responses and established efficacy for RA.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Benlysta® injection [prescribing information]. Rockville, MD: Human Genmome Science Inc./GlaxoSmithKline; December 2021.
2. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis*. 2019;78(6):736-745.
3. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res (Hoboken)*. 2012;64(6):797-808.
4. Stohl W, Merrill JT, McKay JD, et al. Efficacy and safety of belimumab in patients with rheumatoid arthritis: a phase II, randomized, double-blind, placebo-controlled, dose-ranging Study. *J Rheumatol*. 2013;40(5):579-589.

HISTORY

Type of Revision	Summary of Changes	Review Date
New policy	---	05/27/2020
Early Annual Revision	**Lupus Nephritis:** This newly approved condition was added to the policy. For initial therapy the patient must be ≥ 18 years of age. Criteria approve for 6 months for initial therapy (1 year for continuation), if the medication is being used concurrently with at least one other standard therapy unless intolerant. For continuation, the patient must also have demonstrated a response to initial therapy. For all approvals, Benlysta must be prescribed by or in consultation with a specialist.	01/20/2021

	Conditions Not Recommended for Approval: Concurrent use with cyclophosphamide was removed from the Conditions Not Recommended for Coverage (no longer supported in the labeling).	

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, PJIA, PsO, PsA, RA, SJIA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: PJIA, PSA, RA
		IV formulation: PJIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Ilaris (canakinumab SC injection**)**	Inhibition of IL-1β	SJIA
Kineret® (anakinra SC injection)	Inhibition of IL-1	RA, SJIA^
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; PJIA – Polyarticular juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; SJIA – Systemic juvenile idiopathic arthritis; UC – Ulcerative colitis; ^ Off-label use of SJIA supported in guidelines.

PRIOR AUTHORIZATION POLICY

POLICY: Lupus – Benlysta Subcutaneous Prior Authorization Policy

- Benlysta® (belimumab subcutaneous injection – Human Genome Sciences/GlaxoSmithKline)

REVIEW DATE: 01/20/2021

OVERVIEW

Benlysta subcutaneous, a B-lymphocyte stimulator (BLyS)-specific inhibitor, is indicated for the following uses:[1]

- **Lupus nephritis**, in adults with active disease who are receiving standard therapy.
- **Systemic lupus erythematosus** (SLE), in patients ≥ 18 years of age with active, autoantibody-positive, systemic disease in those who are receiving standard therapy.

Benlysta subcutaneous has not been studied and is not recommended in those with severe active central nervous system lupus, or in combination with other biologics. In some of the clinical trials involving Benlysta, Black patients had a lower response rate for the primary endpoint relative to Black patients receiving placebo; therefore, caution is recommended when considering Benlysta in Black patients. Of note, there is also an intravenous formulation of Benlysta with a similar indication except use is expanded to those ≥ 5 years of age.

Guidelines

Benlysta is addressed in the following guidelines:

- **Lupus Nephritis:** Guidelines for lupus nephritis are available from the European league Against Rheumatism (EULAR) and European Renal Association/European Dialysis and Transplant Association (ERA-EDTA) [2019].[3] Benlysta may be considered as add-on treatment for non-responding/refractory lupus nephritis, to facilitate glucocorticoid sparing, control extra-renal lupus activity, and decrease the risk for extra-renal flares.
- **SLE:** Guidelines from the EULAR (2019) recommend consideration of add-on therapy with Benlysta for patients who have an inadequate response to standard of care (e.g., combinations of hydroxychloroquine and glucocorticoids with or without immunosuppressive agents).[2] EULAR defines an inadequate response as residual disease activity not allowing tapering of glucocorticoids and/or frequent relapses.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Benlysta subcutaneous. Because of the specialized skills required for evaluation and diagnosis of patients treated with Benlysta subcutaneous as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Benlysta subcutaneous to be prescribed by or in consultation with a physician who specializes in the condition being treated. Approvals are authorized for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Benlysta subcutaneous is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Lupus Nephritis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following conditions (i, ii, iii, and iv):
     - **i)** Patient is ≥ 18 years of age; AND
     - **ii)** Patient has autoantibody-positive SLE, defined as positive for antinuclear antibodies (ANA) and/or anti-double-stranded DNA (anti-dsDNA) antibody; AND
     - **iii)** Patient meets ONE of the following (a or b):
       - **a)** The medication is being used concurrently with at least one other standard therapy; OR
         Note: Examples of standard therapies include azathioprine, mycophenolate mofetil, cyclophosphamide).

b) Patient is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber; AND

iv) The medication is prescribed by or in consultation with a nephrologist or rheumatologist.

B) Patient is Currently Receiving Benlysta Subcutaneous or Intravenous. Approve for 1 year if the patient meets ALL of the following criteria (i, ii, and iii):

i) Patient meets ONE of the following (a or b):

a) The medication is being used concurrently with at least one other standard therapy; OR
Note: Examples of standard therapies include azathioprine, mycophenolate mofetil, cyclophosphamide).

b) Patient is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber; AND

ii) The medication is prescribed by or in consultation with a nephrologist or rheumatologist; AND

iii) Patient has responded to Benlysta subcutaneous or intravenous, as determined by the prescriber.
Note: Examples of a response include improvement in organ dysfunction, reduction in flares, reduction in corticosteroid dose, decrease of anti-dsDNA titer, and improvement in complement levels (i.e., C3, C4).

2. Systemic Lupus Erythematosus. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets ALL of the following conditions (i, ii, iii, and iv):

i) Patient is ≥ 18 years of age; AND

ii) Patient has autoantibody-positive SLE, defined as positive for antinuclear antibodies (ANA) and/or anti-double-stranded DNA (anti-dsDNA) antibody; AND
Note: Not all patients with SLE are positive for anti-dsDNA, but most will be positive for ANA.

iii) Patient meets ONE of the following (a or b):

a) The medication is being used concurrently with at least one other standard therapy; OR
Note: Examples of standard therapies include an antimalarial (e.g., hydroxychloroquine), systemic corticosteroid (e.g., prednisone), and other immunosuppressants (e.g., azathioprine, mycophenolate mofetil, methotrexate).

b) Patient is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber; AND

iv) The medication is prescribed by or in consultation with a rheumatologist, clinical immunologist, nephrologist, neurologist, or dermatologist.

B) Patient is Currently Receiving Benlysta Subcutaneous or Intravenous. Approve for 1 year if the patient meets ALL of the following criteria (i, ii, and iii):

i) Patient meets ONE of the following (a or b):

a) The medication is being used concurrently with at least one other standard therapy; OR
Note: Examples of standard therapies include an antimalarial (e.g., hydroxychloroquine), systemic corticosteroid (e.g., prednisone), and other immunosuppressants (e.g., azathioprine, mycophenolate mofetil, methotrexate).

b) Patient is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber; AND

ii) The medication is prescribed by or in consultation with a rheumatologist, clinical immunologist, nephrologist, neurologist, or dermatologist; AND

iii) Patient has responded to Benlysta subcutaneous or intravenous, as determined by the prescriber.
Note: Examples of a response include reduction in flares, reduction in corticosteroid dose, decrease of anti-dsDNA titer, improvement in complement levels (i.e., C3, C4), or

improvement in specific organ dysfunction (e.g., musculoskeletal, blood, hematologic, vascular, others).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Benlysta subcutaneous is not recommended in the following situations:

138. Concurrent Use with Other Biologics. Benlysta has not been studied and is not recommended in combination with other biologics.[1] Safety and efficacy have not been established with these combinations. See APPENDIX for examples of other biologics that should not be taken in combination with Benlysta.

139. Rheumatoid Arthritis. A Phase II dose-ranging study evaluating patients with rheumatoid arthritis showed only small ACR 20 responses with Benlysta (e.g., ACR 20 response at Week 24 was 28% with Benlysta 10 mg/kg).[4] Numerous other agents are available with higher ACR responses and established efficacy for rheumatoid arthritis.

140. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

5. Benlysta® injection [prescribing information]. Rockville, MD: Human Genmome Science Inc./GlaxoSmithKline; January 2020.
6. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis*. 2019;78(6):736-745..
7. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res (Hoboken)*. 2012;64(6):797-808.
8. Stohl W, Merrill JT, McKay JD, et al. Efficacy and safety of belimumab in patients with rheumatoid arthritis: a phase II, randomized, double-blind, placebo-controlled, dose-ranging Study. *J Rheumatol*. 2013;40(5):579-589.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Systemic Lupus Erythematosus:** For patients continuing on therapy with Benlysta, the requirement that the patient is ≥ 18 years of age was removed from the policy. This age criterion now only applies to those initiating therapy with Benlysta SC.	05/09/2019
Annual Revision	**Systemic Lupus Erythematosus:** Clarify in criteria that autoantibody-positive SLE is defined as patients who are positive for antinuclear antibodies (ANA) and/or anti-double-stranded DNA antibody (previously this was listed as an i.e. in the criteria). Examples standard therapies were moved to a Note in the criteria section (previously listed within the criteria). For the exceptions applying to patients with an intolerance to standard therapy, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). Examples of a response to therapy were moved to a note (previously included within the criteria).	05/27/2020
Early Annual Revision	**Lupus Nephritis:** This newly approved condition was added to the policy. For initial therapy the patient must be ≥ 18 years of age. Criteria approve for 6 months for initial therapy (1 year for continuation), if the medication is being used concurrently with at least one other standard therapy unless intolerant. For continuation, the patient must also have also demonstrated a response to initial therapy. For all approvals, Benlysta much be prescribed by or in consultation with a specialist. **Conditions Not Recommended for Coverage:** Concurrent use with cyclophosphamide intravenous was removed from the Conditions Not Recommended for Coverage (no longer supported in the labeling).	01/20/2021

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, PJIA, PsO, PsA, RA, SJIA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: PJIA, PSA, RA
		IV formulation: PJIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Ilaris (canakinumab SC injection**)**	Inhibition of IL-1β	SJIA
Kineret® (anakinra SC injection)	Inhibition of IL-1	RA, SJIA^
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; PJIA – Polyarticular juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; SJIA – Systemic juvenile idiopathic arthritis; UC – Ulcerative colitis; ^ Off-label use of SJIA supported in guidelines.

PRIOR AUTHORIZATION POLICY

POLICY: Lupus – Lupkynis Prior Authorization Policy

- Lupkynis™ (voclosporin capsules – Aurinia)

REVIEW DATE: 01/27/2021

OVERVIEW

Lupkynis, a calcineurin inhibitor immunosuppressant, is indicated in combination with a background immunosuppressive therapy regimen for the treatment of adults with active **lupus nephritis**.[1] Safety and efficacy have not been established in combination with cyclophosphamide and is not recommended. The recommended starting dose is 23.7 mg twice daily taken on an empty stomach, used in combination with

mycophenolate mofetil and corticosteroids. Dose modifications are required based on estimated glomerular filtration rate (eGFR). Lupkynis is not recommended if baseline eGFR is ≤ 45 mL/min/1.73 m^2 unless the benefit exceeds the risk. If therapeutic benefit is not apparent by Week 24, consider discontinuation of Lupkynis.

Guidelines

Guidelines for lupus nephritis from EULAR/ERA-EDTA (European League Against Rheumatism-European Renal Association-European Dialysis and Transplant Association) [2019] recommend treatment based on disease classification.[2] Patient survival, long-term preservation of kidney function, and prevention of organ damage are among the goals of treatment. First-line initial therapy for patients with class III or IV disease (± class V) includes mycophenolate mofetil or intravenous cyclophosphamide, in combination with glucocorticoids. In pure class V disease, the first-line choice is mycophenolate mofetil + glucocorticoids. Following a response to initial therapy, mycophenolate mofetil or azathioprine (± low-dose glucocorticoids) are the drugs of choice for subsequent immunosuppressive treatment. Mycophenolate mofetil in combination with a calcineurin inhibitor (especially tacrolimus) are among the alternative therapies for those with nephrotic-range proteinuria or for class V nephritis.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lupkynis. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lupkynis as well as the monitoring required for adverse events and long-term efficacy, approval requires Lupkynis to be prescribed by or in consultation with a physician who specializes in the condition being treated. Approvals are authorized for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lupkynis is recommended in those who meet the following criteria:

FDA-Approved Indications

3. Lupus Nephritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following conditions (i, ii, iii, iv, and v):
- **i)** Patient is ≥ 18 years of age; AND
- **ii)** Patient has autoantibody-positive systemic lupus erythematosus (SLE), defined as positive for antinuclear antibodies (ANA) and/or anti-double-stranded DNA (anti-dsDNA) antibody; AND
- **iii)** Patient meets ONE of the following (a or b):
  - **a)** The medication is being used concurrently with mycophenolate mofetil and a systemic corticosteroid; OR
  - **b)** According to the prescriber, patient is not a candidate for mycophenolate mofetil and a systemic corticosteroid due to inadequate efficacy OR significant intolerance with these medications; AND
- **iv)** Patient has an estimated glomerular filtration rate (eGFR) > 45 mL/min/m^2; AND
- **v)** The medication is prescribed by or in consultation with a nephrologist or rheumatologist.

B) Patient is Currently Receiving Lupkynis. Approve for 1 year if the patient meets ALL of the following criteria (i, ii, iii, and iv):
- **i)** Patient is ≥ 18 years of age; AND
- **ii)** Patient meets ONE of the following (a or b):

a) The medication is being used concurrently with mycophenolate mofetil and a systemic corticosteroid; OR

b) According to the prescriber, patient is not a candidate for mycophenolate mofetil and a systemic corticosteroid due to inadequate efficacy OR significant intolerance with these medications; AND

iii) The medication is prescribed by or in consultation with a nephrologist or rheumatologist; AND

iv) Patient has responded to Lupkynis, as determined by the prescriber.
Note: Examples of a response include improvement in organ dysfunction, reduction in flares, reduction in corticosteroid dose, decrease of anti-dsDNA titer, and improvement in complement levels (i.e., C3, C4).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lupkynis is not recommended in the following situations:

141. **Concurrent Use with Biologics or with Cyclophosphamide.** Lupkynis has not been studied in combination with other biologics or cyclophosphamide.[1] Safety and efficacy have not been established with these combinations. See APPENDIX for examples of biologics that should not be taken in combination with Lupkynis.

142. **Plaque Psoriasis.** In a Phase III trial, voclosporin was inferior to cyclosporine, which is an established therapy for plaque psoriasis.[3,4] Numerous other FDA-approved therapies are available with established efficacy for plaque psoriasis.

143. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

9. Lupkynis™ capsules [prescribing information]. Rockville, MD: Aurinia; January 2021.
10. Franouriakis A, Kostopoulou M, Cheema K, et al. 2019 Update of the Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. *Ann Rheum Dis*. 2020;79(6):713-723.
11. Li Y, Palmisano M, Sun D, Zhou Sl. Pharmacokinetic disposition difference between cyclosporine and voclosporin drives their distinct efficacy and safety profiles in clinical studies. *Clin Pharmacol*. 2020;12:83-96.
12. US National Institutes of Health. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2021 Jan 21]. Available from: https://clinicaltrials.gov/. Search term: voclosporin.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/27/2021

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Benlysta™ (belimumab SC injection, belimumab IV infusion)	BLyS-specific inhibitor	SLE, lupus nephritis
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, PsO, PsA, RA

Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, PJIA, PsO, PsA, RA, SJIA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: PJIA, PSA, RA
		IV formulation: PJIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Ilaris (canakinumab SC injection**)**	Inhibition of IL-1β	SJIA
Kineret® (anakinra SC injection)	Inhibition of IL-1	RA, SJIA^
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; IV – Intravenous; BLyS – B-lymphocyte stimulator; SLE – Systemic lupus erythematosus; TNF – Tumor necrosis factor; IL – Interleukin; PDE4 – Phosphodiesterase 4; AS – Ankylosing spondylitis; CD – Crohn's disease; PJIA – Polyarticular juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; SJIA – Systemic juvenile idiopathic arthritis; UC – Ulcerative colitis; ^ Off-label use of SJIA supported in guidelines.

PRIOR AUTHORIZATION POLICY

POLICY: Lyrica® CR (pregabalin extended-release tablets – Pfizer)

DATE REVIEWED: 03/04/2020

OVERVIEW

Lyrica CR is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN).[1] The efficacy of Lyrica CR has not been established for the management of fibromyalgia or as adjunctive therapy for adults with partial onset seizures. Lyrica CR is an analog of the neurotransmitter gamma-aminobutyric acid (GABA). Lyrica CR is dosed once daily (QD), and it is a Schedule V controlled substance.

Gabapentin immediate-release (IR) [Neurontin, generics] is also a GABA analog.[2] Gabapentin is indicated for the management of PHN in adults and as adjunctive therapy in the treatment of partial onset seizures, with and without secondary generalization, in adults and pediatric patients ≥ 3 years of age with epilepsy. Gabapentin IR has been used off-label extensively and is included as a treatment option in various guidelines. Pregabalin immediate-release capsules and oral solution are approved for neuropathic pain associated with DPN, PHN, adjunctive therapy for the treatment of partial onset seizures in patients ≥ 1 month of age, fibromyalgia, and neuropathic pain associated with spinal cord injury.[3] Like Lyrica CR, pregabalin immediate-release is a Schedule V controlled substance.

Disease Overview

These drugs exert their pharmacologic action by binding to the alpha-2-delta subunit of voltage-gated calcium channels.[4] The binding of this subunit reduces the release of several neurotransmitters including glutamate, noradrenaline, and substance P.

PHN is the persistence of the pain of herpes zoster > 3 months after resolution of the rash; it is relatively common, affecting 10 to 15% of those with herpes zoster.[5] The time interval used in the clinical case definition of PHN varies in the literature from 1 to 6 months after resolution of the rash. The incidence of PHN increases with age. The duration of PHN is highly variable; in one longitudinal study, only 48% of patients who developed PHN were symptomatic 1 year after onset. Thus, the natural history of resolution of PHN over time is a confounder in the evaluation of treatment efficacy and may limit the ability to generalize the results of controlled clinical trials in this population. Administration of antiviral agents within 72 hours of the onset of herpes zoster can reduce the intensity and duration of acute illness, and can prevent PHN. Efforts to prevent herpes zoster and PHN are important in that 40% to 50% of patients with PHN do not respond to any treatment.

The diabetic neuropathies are a heterogeneous group of disorders with diverse clinical manifestations.[6] The early recognition and appropriate management of neuropathy in the patient with diabetes is important. Diabetic neuropathy is a diagnosis of exclusion. Up to 50% of diabetic peripheral neuropathy (DPN) may be asymptomatic. Painful diabetic neuropathy (PDN) affects 16% of patients with diabetes, and it is frequently unreported (12.5%) and more frequently untreated (39%).[7] If not recognized and if preventive foot care is not implemented, patients are at risk for injuries to their insensate feet.[6] Recognition and treatment of autonomic neuropathy may improve symptoms, reduce sequelae, and improve quality of life. Glycemic control can effectively prevent DPN in type 1 diabetes and may modestly slow their progression in type 2 diabetes but does not reverse neuronal loss. Therapeutic strategies (pharmacologic and nonpharmacologic) for the relief of painful DPN can potentially reduce pain and improve quality of life.

Clinical Efficacy

Support for the efficacy of Lyrica CR for the management of PHN and DPN was based on the efficacy of IR Lyrica for these indications, along with one study of Lyrica CR in adults with PHN.[1] This 19-week, randomized, withdrawal study compared Lyrica CR 82.5 mg, 165 mg, 247.5 mg, 330 mg, 495 mg, or 660 mg QD with placebo. Those enrolled were required to have pain present for > 3 months after healing of the herpes zoster skin rash and a baseline pain score ≥ 4 on the numeric rating scale (NRS)-Pain (assessed over a 1 week recall period). Patients who responded to treatment in the single-blind phase of the study (≥ 50% reduction in pain) moved into the double-blind phase and were randomized to the Lyrica CR dose achieved in the single-blind phase or placebo. Patients were treated for ≤ 3 months following randomization. Lyrica CR demonstrated statistically significant improvement in the efficacy endpoint of change in mean pain score from baseline compared with placebo. In the Lyrica CR arm, 80% of patients achieved ≥ 30% improvement and 74% of patients achieved ≥ 50% improvement in pain intensity. In the placebo group, 65% of patients achieved ≥ 30% improvement and 55% of patients achieved ≥ 50% improvement in pain intensity.

Guidelines

Various guidelines for the treatment of DPN, neuropathic pain, PHN, and restless legs syndrome recommend gabapentin or pregabalin immediate-release as treatment options.[5-14] Guidelines have not been updated to address Lyrica CR.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Lyrica CR. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lyrica CR is recommended in those who meet the following criteria:

FDA-Approved Indications

27. Neuropathic Pain Associated with Diabetic Peripheral Neuropathy (DPN). Approve Lyrica CR for 1 year if the patient the patient meets ONE of the following criteria (A or B):
- **A)** Patient has tried gabapentin immediate-release (brand [Neurontin] or generic) or generic pregabalin; OR
- **B)** Patient is currently established on therapy with Lyrica CR.

28. Postherpetic Neuralgia. Approve Lyrica CR for 1 year if the patient meets ONE of the following criteria (A or B):
- **A)** Patient has tried gabapentin immediate-release (brand [Neurontin] or generic) or generic pregabalin; OR
- **B)** Patient is currently established on therapy with Lyrica CR.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Lyrica CR has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

144. Fibromyalgia. A double-blind, placebo-controlled, randomized withdrawal trial of Lyrica CR in adults with fibromyalgia failed to demonstrate efficacy.[1]

145. Partial Onset Seizures. A double-blind, placebo-controlled, randomized trial of Lyrica CR as adjunctive therapy in adults with partial onset seizures failed to demonstrate efficacy.[1]

146. Restless Legs Syndrome. No data are available for Lyrica CR for the treatment of restless legs at this time.

147. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	02/14/2018
Annual revision	No change to criteria.	02/20/2019
Selected revision	For both FDA-approved uses (Neuropathic Pain Associated with Diabetic Peripheral Neuropathy and Postherpetic Neuralgia), generic pregabalin was added as one of the possible required medications to be tried prior to approval of Lyrica CR.	08/07/2019
Annual revision	No change to criteria.	03/04/2020

PRIOR AUTHORIZATION POLICY

POLICY: Makena (hydroxyprogesterone caproate) Prior Authorization Policy

- Makena® (hydroxyprogesterone caproate injection [subcutaneous and intramuscular] – AMAG Pharmaceuticals, generics [intramuscular only])

REVIEW DATE: 09/30/2020

OVERVIEW

Makena is an injectable progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.[1] The effectiveness of Makena is based on improvement in the proportion of women who delivered < 37 weeks of gestation. There are no clinical trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity. While there are many risk factors for preterm birth, safety and efficacy of Makena has been demonstrated only in women with a prior spontaneous singleton preterm birth. It is not intended for use in women with multiple gestations or other risk factors for preterm birth. Makena is administered by the intramuscular route at a dose of 250 mg (1 mL) once weekly or by the subcutaneous route using an auto-injector at a dose of 275 mg (1.1 mL) once weekly; both products require administration by a healthcare professional. Generic Makena, hydroxyprogesterone caproate injection, is available for IM administration only. Makena should be administered beginning between 16 weeks, 0 days and 20 weeks, 6 days gestation and continued once weekly until week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever occurs first.

GUIDELINES

As of October 2019, the American College of Obstetricians and Gynecologists continues to recommend progesterone supplementation starting at 16 to 24 weeks of gestation to women with a singleton gestation and a prior spontaneous preterm birth.[2,3] The Society for Maternal-Fetal Medicine statement on the use of 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth (2019) states it is reasonable to use 17-alpha hydroxyprogesterone caproate in women with a very-high-risk profile.[4] For women at risk of recurrent spontaneous preterm birth, the risk-benefit discussion should incorporate a shared decision-making approach.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Makena (hydroxyprogesterone caproate). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Makena (hydroxyprogesterone caproate) and generics are recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Reduce Risk of Preterm Birth.** Approve for up to 5 months of therapy (21 injections) in patients who meet the following criteria (A, B, and C):
   - **A)** Patient is pregnant with a singleton pregnancy; AND
   - **B)** Patient has a history of singleton spontaneous preterm birth prior to 37 weeks gestation; AND
   - **C)** Treatment will begin in patients who are at least 16 weeks, 0 days of gestation, according to the prescribing physician or other prescriber.

   Note: In cases where there was an inaccuracy in dating the pregnancy, a one-month authorization may be granted to patients who have already received 21 injections and are < 37 weeks pregnant.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Makena (hydroxyprogesterone caproate) is not recommended in the following situations:

1. **History of a Threatened Preterm Birth.** Makena is not indicated in pregnant women who experienced a past threatened preterm birth but delivered a full-term infant after 36 completed weeks gestation.[1]

2. **Infertility.** Some studies have evaluated hydroxyprogesterone caproate as the progesterone used for *in vitro* fertilization.[5,6] However, progesterone in oil or vaginally administered progesterone are mentioned for use during the luteal phase and in early pregnancy in the treatment of infertility by an educational bulletin by the Practice Committee of the American Society of Reproductive Medicine.[7]

3. **Patients Pregnant with Multiple Gestations.** Makena is not indicated in patients pregnant with multiple gestations (e.g., twins, triplets, or other multiples).[1] Hydroxyprogesterone caproate has failed to decrease preterm birth in women pregnant with twins and triplets.[8-10] In a randomized, double-blind, placebo-controlled study in 661 women, delivery or fetal death prior to Week 35 occurred in 41.5% of women pregnant with twins in the hydroxyprogesterone caproate group compared to 37.3% of those pregnant with twins in the placebo group (relative risk [RR]: 1.1; 95% confidence interval [CI]: 0.9, 1.5).[8] In a randomized, double-blind, placebo-controlled study in women pregnant with triplets (n = 134), treatment with hydroxyprogesterone caproate did not affect the rate of delivery or fetal loss prior to Week 35 (RR: 1.0; 95% CI: 0.9, 1.1).[9] In an another randomized, double-blind, placebo-controlled study, 56 women pregnant with triplets were assigned to treatment with hydroxyprogesterone caproate and 25 women were assigned to placebo.[10] There was not a significant difference in delivery prior to Week 28, 32, or 35 in either treatment group; however, significantly more stillbirths/miscarriages occurred in the hydroxyprogesterone group (8%) compared to no stillbirths/miscarriages in the placebo group (P = 0.01). In one randomized, double-blind, controlled trial in unselected women with twin pregnancies, intramuscular 17P (not Makena; another marketed product in Europe) did not reduce preterm birth before 37 weeks of gestation; however, it did reduce neonatal morbidity parameters and also increased birthweight.[11] Other studies in women with multiple gestations (primarily twin gestations) have not shown a prolonged gestation or a reduction in neonatal morbidity with 17P compared with placebo.[12-14]

4. **Pregnant Patient with Short Cervix Without a History of a Prior Singleton Spontaneous Preterm Birth.** Makena is not indicated for use in pregnant women with short cervix and no history of singleton SPTB prior to 37 weeks gestation.[1]

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Selected Revision	Added Makena for subcutaneous use; added Without a History of a Prior Singleton SPTB to the exclusion Pregnant Patient with a Short Cervix.	3/7/2018
Annual Revision	No criteria changes. Generic intramuscular product added.	8/29/2018
Annual Revision	No criteria changes.	9/04/2019
Annual Revision	No criteria changes.	9/30/2020

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Carbaglu Prior Authorization Policy

- Carbaglu (carglumic acid tablets for oral suspension – Orphan Europe, SARL/Recordati Rare Diseases)

REVIEW DATE: 03/03/2021

OVERVIEW

Carbaglu, a carbamoyl phosphate synthetase 1 (CPS 1) activator, is indicated in adults and pediatric patients for the following conditions:[1]

- **N-acteylglutamate synthase (NAGS) deficiency** with chronic hyperammonemia or acute hyperammonemia (as adjunct therapy to standard of care).
- **Propionic acidemia or methylmalonic acidemia** with acute hyperammonemia (as adjunct therapy to standard of care).

For NAGS deficiency, the prescribing information notes that treatment with Carbaglu should be initiated as soon as the disorder is suspected, which may be as soon as birth.[1]

For acute hyperammonemia due to propionic acidemia or methylmalonic acidemia, Carbaglu is indicated as adjunctive therapy for acute treatment.[1] In this setting, Carbaglu should be continued until the patient's ammonia level is < 50 micromol/L and for a maximum duration of 7 days.

Disease Overview

NAGS Deficiency

Carbaglu is a synthetic analog of N-acetylglutamate, which activates CPS 1, the first reaction in the urea cycle.[1] The function of the urea cycle is to convert ammonia into urea for urinary excretion. In the case of NAGS deficiency, N-acetylglutamate is not sufficiently produced due to lack of the NAGS enzyme.[2] NAGS deficiency is the rarest urea cycle disorder with an estimated incidence of less than 1:2,000,000 live births. Age of diagnosis can vary from neonatal to adulthood; based on literature review, most cases present in the early neonatal period. Therefore, newborn screening is of limited value as patients are likely to be symptomatic before screening results are available. Common presenting features include poor feeding, vomiting, lethargy, decreased consciousness, seizures, and hypotonia. Laboratory abnormalities include hyperammonemia which can lead to significant morbidity and mortality in severe cases. Genetic testing is required to confirm the diagnosis; however, given the delays involved with genetic testing, it has been suggested that a therapeutic trial of Carbaglu should be initiated for any patient with unexplained hyperammonemia.

Propionic Acidemia and Methylmalonic Acidemia

In propionic and methylmalonic acidemias, other enzymatic defects result in accumulation of propionyl-coenzyme A (CoA), which acts as a competitive inhibitor for NAGS.[3,4] The incidence of propionic acidemia is 1:100,000 to 1:150,000, and the incidence of methylmalonic acidemia is 1:50,000.[3] According to guidelines for management of propionic acidemia and methylmalonic acidemia (2014), these disorders should be considered in any newborn/child (critically ill or not) with unexplained metabolic acidosis (with elevated anion gap); elevated lactate; hyperammonemia; leukopenia, thrombocytopenia, anemia; and/or urine ketone bodies. If ammonia is increased, further metabolic investigations should be performed immediately but specific treatment must not be delayed. Carbaglu is supported as part of the initial management plan for symptomatic hyperammonemia both in patients with known propionic/methylmalonic acidemia and in undiagnosed patients. Other elements of initial management include cessation of protein intake, use of intravenous glucose and insulin, and other medications such as carnitine and vitamin B_{12}. Extracorporeal detoxification (i.e., dialysis) may be used in some cases, particularly for extremely elevated ammonia levels.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Carbaglu. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Carbaglu as well as the monitoring required for adverse events and long-term efficacy, approval requires Carbaglu to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Carbaglu is recommended in those who meet the following criteria:

FDA-Approved Indications

118. N-Acetylglutamate Synthase Deficiency with Hyperammonemia. Approve for the duration noted below if the patient meets ALL of the following criteria (A, B, and C):

A) According to the prescriber, diagnosis is supported by one of the following (i or ii):

i. Approve for 1 year if genetic testing confirmed a mutation leading to N-acetylglutamate synthase deficiency; OR

ii. Approve for 3 months if the patient has hyperammonemia diagnosed with an ammonia level above the upper limit of the normal reference range for the reporting laboratory.
Note: Reference ranges are dependent upon patient's age; AND

B) The medication is prescribed in conjunction with a protein-restricted diet; AND

C) The medication is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).

119. Propionic Acidemia or Methylmalonic Acidemia with Hyperammonemia, Acute Treatment. Approve for 7 days if the patient meets the following criteria (A, B, and C):

A) Patient's plasma ammonia level is ≥ 50 micromol/L; AND

B) The medication is prescribed in conjunction with other ammonia-lowering therapies; AND
Note: Examples of other ammonia-lowering therapies include intravenous glucose, insulin, L-carnitine, protein restriction, and dialysis.

C) The medication is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Carbaglu is not recommended in the following situations:

126. Propionic Acidemia or Methylmalonic Acidemia with Hyperammonemia, Maintenance. Chronic use of Carbaglu (beyond 7 days) for propionic acidemia or methylmalonic acidemia is not indicated.[1] There is no clinical evidence for long-term use of Carbaglu in propionic acidemia or methylmalonic acidemia.[3]

127. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	03/13/2019
Annual Revision	**N-Acetylglutamate Synthase (NAGS) Deficiency with Hyperammonemia:** For criterion that approves if the patient has hyperammonemia, clarify that this is according to laboratory testing.	03/11/2020
Annual Revision	**Propionic Acidemia or Methylmalonic Acidemia with Hyperammonemia, Acute Treatment:** This condition was added to FDA-approved indications based on updated labeling. **Propionic Acidemia or Methylmalonic Acidemia with Hyperammonemia, Maintenance:** This condition was added to Conditions Not Recommended for Approval.	03/03/2021

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Cysteamine (Oral) Products

- Cystagon (cysteamine bitartrate capsules – Mylan Pharmaceuticals)
- Procysbi (cysteamine bitartrate delayed-release capsule, delayed release granules – Raptor Therapeutics Inc.)

DATE REVIEWED: 03/11/2020

OVERVIEW

Cystagon and Procysbi are cystine-depleting agent indicated for the management of nephropathic cystinosis in adults and children.[1-2] Note that Procysbi is indicated specifically in patients who are 1 year of age and older.[1] Therapy with a cysteamine product should be initiated promptly once the diagnosis is confirmed (i.e., increased white blood cell cystine concentration). Cystagon needs to be administered four times daily, whereas Procysbi (a delayed-release formulation of cysteamine) is given once every 12 hours.[1-2] For patients who are unable to swallow capsules, both products have instructions for opening the capsules and administering in food and/or liquids.

Disease Overview

Cystinosis is a very rare autosomal recessive inborn error of metabolism in which the transport of cystine out of lysosomes is abnormal.[3-5] As a result of deficient or absent cystinosin (which normally transports cystine out of the lysosome),

cystine accumulates within lysosomes and forms crystals in many tissues, including the kidneys, liver, bone marrow, pancreas, muscle, rectal mucosa, brain and eye. Diagnosis is confirmed by measuring cystine levels in polymorphonuclear leukocytes.[6] Molecular genetic testing idenitifies a characteristic mutation of the *CTNS* gene. Prenatal diagnosis is possible (i.e., by elevation of cystine in amniotic fluid or chorionic villi). Patients with cystinosis also experience growth failure and rickets, and cystine deposits in the cornea cause photophobia.[3-5] Over time, most organs are damaged. Cysteamine products are aminothiols that act as cystine-depleting agents.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of cysteamine oral products (Cystagon and Procysbi). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with cysteamine oral products (Cystagon and Procysbi) as well as the monitoring required for adverse events and long-term efficacy, approval requires cysteamine oral products (Cystagon and Procysbi) to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of cysteamine oral products (Cystagon and Procysbi) is recommended in those who meet the following criteria:

FDA-Approved Indications

120. Cystinosis, Nephropathic. Approve for 1 year if the patient meets the following criteria (A, B, and C):

A) According to the prescriber, the diagnosis was confirmed by one of the following (i or ii):

i. Genetic testing confirmed a mutation of the *CTNS* gene; OR

ii. White blood cell cystine concentration above the upper limit of the normal reference range for the reporting laboratory.

Note: The methods used for measuring cystine vary among individual laboratories and depend upon the assay method used by the individual laboratory; values obtained from using different assay methods may not be interchangeable; AND

B) The patient will not be using Cystagon and Procysbi concurrently; AND

C) The medication is prescribed by or in consultation with a nephrologist or a metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Cysteamine oral products (Cystagon and Procysbi) have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

128. Concomitant Therapy with Cystagon and Procysbi. There are no data available to support concomitant use.

129. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

402. Procysbi [prescribing information]. Lake Forest, IL: Horizon Pharma; May 2019.
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404. Wilmer MJ, Schoeber JP, van den Heuvel LP, Levtchenko EN. Cystinosis: practical tools for diagnosis and treatment. *Pediatr Nephrol*. 2011; 26(2): 205–215.
405. Tsilou E, Zhou M, Gahl W, et al. Ophthalmic manifestations and histopathology of infantile nephropathic cystinosis: Report of a case and review of the literature. *Surv Ophthalmol*. 2007;52(1):97–105.
406. Gahl WA, Thoene JG, Schneider JA, et al. NIH Conference. Cystinosis: progress in a prototypic disease. *Ann Int Med*. 1988;109:557-569.
407. National Organization for Rare Disorders (NORD). Cystinosis. Accessed on February 25, 2020. Available at: https://rarediseases.org/rare-diseases/cystinosis/.

HISTORY

Type of Revisior	Summary of Changes	Date Reviewed
New Policy	--	03/13/2019
Annual revision	No criteria changes,	03/11/2020

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Cysteamine Ophthalmic Solution Prior Authorization Policy

- Cystadrops® (cysteamine 0.37% ophthalmic solution – Recordati Rare Diseases)
- Cystaran® (cysteamine 0.44% ophthalmic solution – Leadiant Biosciences)

REVIEW DATE: 03/11/2020; selected revision 09/16/2020

OVERVIEW

Cystamine ophthalmic solution is a cystine-depleting agent indicated for the treatment of corneal cystine crystal accumulation in patients with cystinosis.[1,2] The recommended dose is one drop into each eye four times daily during waking hours (Cystadrops) or one drop into each eye every waking hour (Cystaran).

Disease Overview

Cystinosis is a rare autosomal recessive inborn error of metabolism in which the transport of cystine out of lysosomes is abnormal.[3-5] As a result of deficient or absent cystinosin (which normally transports cystine out of the lysosome), cystine accumulates within lysosomes and forms crystals in many tissues, including the kidneys, liver, bone marrow, pancreas, muscle, rectal mucosa, brain and eye. Patients with cystinosis also experience growth failure and rickets, and cystine deposits in the cornea cause photophobia. With time, most organs are damaged. Patients may present only with corneal crystal deposition but no associated systemic manifestations; the kidney, retina, and other organs are free of cystine accumulation in these patients. In patients without systemic symptoms, diagnosis of ocular cystinosis is often in adulthood when corneal crystal deposits are noted on ocular examination.[6] Of note, with oral cysteamine the concentration obtained in corneal tissue is inadequate and does not affect corneal cystine crystals. Topical treatment is required to dissolve existing cystine crystals.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of cystamine ophthalmic solution. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with cystamine ophthalmic solution as well as the monitoring required for adverse events and long-term efficacy, approval requires cystamine ophthalmic solution to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of cystamine ophthalmic solution is recommended in those who meet the following criteria:

FDA-Approved Indications

121. Cystinosis, Corneal Cysteine Crystal Deposits. Approve for 1 year if the patient meets the following criteria (A and B):

- **A)** The patient has corneal cysteine crystal deposits confirmed by slit-lamp examination; AND
- **B)** The agent is prescribed by or in consultation with an ophthalmologist or a metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of cystamine ophthalmic solution is recommended in those who meet the following criteria:

130. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

408. Cystadrops [prescribing information]. Lebanon, NJ: Recordati Rare Diseases; August 2020.
409. Cystaran [prescribing information]. Gaithersburg, MD: Leadiant Biosciences; May 2018.
410. Wilmer MJ, Schoeber JP, van den Heuvel LP, Levtchenko EN. Cystinosis: practical tools for diagnosis and treatment. *Pediatr Nephrol*. 2011; 26(2): 205–215.
411. Tsilou E, Zhou M, Gahl W, et al. Ophthalmic manifestations and histopathology of infantile nephropathic cystinosis: Report of a case and review of the literature. *Surv Ophthalmol.* 2007;52(1):97–105.
412. Gahl WA, Thoene JG, Schneider JA, et al. NIH Conference. Cystinosis: progress in a prototypic disease. *Ann Int Med.* 1988;109:557-569.

413. Biswas S, Gaviria M, Malheiro L, et al. Latest clinical approaches in the ocular management of cystinosis: a review of current practice and opinion from the ophthalmology cystinosis forum. *Ophthalmol Ther*. 2018;7(2):307-322.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	03/13/2019
Annual Revision	No criteria changes.	03/11/2020
Selected Revision	Cystadrops were added to the policy. Existing criteria for Cystaran also apply Cystadrops.	09/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Dojolvi Prior Authorization Policy

- Dojolvi™ (triheptanoin oral liquid – Ultragenyx)

REVIEW DATE: 07/22/2020; selected revision 11/11/2020

OVERVIEW

Dojolvi, a synthetic medium odd-chain triglyceride, is indicated as a source of calories and fatty acids for the treatment of adults and pediatric patients with molecularly **confirmed long-chain fatty acid oxidation disorders (LC-FAODs)**.[1]

For patients receiving another medium-chain triglyceride product, discontinue prior to the first dose of Dojolvi.

Disease Overview

LC-FAODs are a group of autosomal recessive genetic metabolic disorders in which the body is unable to properly oxidize long-chain fatty acid in the mitochondria (normally an important energy pathway when glucose is low).[2,3] The four most commonly affected enzymes are carnitine palmitoyl transferase 2 (CPT-2), very long-chain acyl-CoA dehydrogenase (VLCAD), long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), and mitochondrial trifunctional protein (TFP).[4] Other less common mutations may also occur.[2,4] Onset may occur anywhere from the neonatal period to adulthood. Clinical manifestations are heterogeneous and not well correlated with genotype.[2] Diagnosis of LC-FAODs has increased with the use of routine newborn screening. Newborn screening tests measure acylcarnitines in dried blood spots.[5] Abnormal newborn screening results or the presence of symptoms associated with LC-FAODs warrant further evaluation involving plasma acylcarnitine measurement, enzyme activity assays, and/or genetic testing. The activity of specific enzymes can be measured in lymphocytes or skin fibroblasts since these cells express all enzymes involved in long-chain fatty acid oxidation.[3] Mutation analysis can identify the specific genetic defect. However, new mutations and variants are regularly identified, requiring functional studies such as enzyme activity measurements for confirmation of the diagnosis.

Guidelines

A consensus statement regarding treatment recommendations in LC-FAODs was published in 2009; Dojolvi is not specifically addressed, although medium-chain triglycerides (MCT) are discussed more broadly.[6] Dietary recommendations are provided for VLCAD deficiency but it is noted that these can also be applied to similar disorders, such as CPT-2 deficiency. For symptomatic patients with VLCAD deficiency, long-chain fat content of the diet is suggested to be 25% to 30% of total energy. The diet should be enriched with MCT to provide 20% of total energy from MCT. In asymptomatic VLCAD deficiency, the necessity of dietary long-chain fat restriction is under debate. Per the consensus statement, the current recommendation is to mildly reduce fat content to 30% to 40% of total energy in these patients. However, it is noted that the clinical course is not predictable. Even for patients in whom long-chain triglyceride restriction is deemed unnecessary, MCT supplementation (especially prior to exercise) may still be needed. For LCHAD and TFP deficiency, both symptomatic and asymptomatic patients should follow long-chain fat restriction with MCT supplementation.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Dojolvi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Dojolvi as well as the monitoring required for adverse events and long-term efficacy, approval requires Dojolvi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Dojolvi is recommended in those who meet the following criteria:

FDA-Approved Indications

122. Long-Chain Fatty Acid Oxidation Disorders. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):

- **A)** Patient has a molecularly confirmed diagnosis of a long-chain fatty acid oxidation disorder based on at least TWO of the following (TWO of i, ii, or iii):
  - **i.** Disease-specific elevations of acylcarnitines on a newborn blood spot or in plasma; OR
  - **ii.** Enzyme activity assay (in cultured fibroblasts or lymphocytes) below the lower limit of the normal reference range for the reporting laboratory; OR
    Note: Examples of enzyme assays include carnitine palmitoyl transferase 2 (CPT-2), very long-chain acyl-CoA dehydrogenase (VLCAD), long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), and mitochondrial trifunctional protein (TFP).
  - **iii.** Genetic testing demonstrating pathogenic mutation in a gene associated with long-chain fatty acid oxidation disorders; AND
    Note: Examples of genes associated with long-chain fatty acid disorders include *CPT2* (encodes CPT-2), *ACADVL* (encodes VLCAD), *HADHA* (encodes LCHAD and TFP), and *HADHB* (encodes TFP).
- **B)** Patient will not use any other medium-chain triglyceride products concomitantly with Dojolvi; AND
- **C)** Patient meets at least one of the following (i, ii, or iii):
  - **i.** According to the prescriber, the patient has had inadequate efficacy or significant intolerance to an over-the-counter (nutraceutical supplements) medium-chain triglyceride product (other than Dojolvi); OR
  - **ii.** According to the prescriber, the patient has a history of at least one severe or recurrent manifestation of long-chain fatty acid oxidation disorders (i.e., cardiomyopathy, rhabdomyolysis, or hypoglycemia); OR
  - **iii.** Patient is currently receiving Dojolvi; AND
- **D)** The medication is prescribed by, or in consultation with, a metabolic disease specialist or a physician who specializes in the management of long-chain fatty acid oxidation disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Dojolvi is not recommended in the following situations:

131. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

414. Dojolvi™ [prescribing information]. Novato, CA: Ultragenyx; June 2020.
415. Merritt JL II, Norris M, Kanungo S. Fatty acid oxidation disorders. *Ann Transl Med.* 2018;6(24):473.
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417. Vockley J, Burton B, Berry GT, et al. UX007 for the treatment of long chain-fatty acid oxidation disorders: safety and efficacy in children and adults following 24 weeks of treatment. *Mol Genet Metab.* 2017;120(4):370-77.
418. ACT Sheets and Algorithms: Newborn Screening ACT Sheets and Algorithms. American College of Molecular Genetics and Genomics. Available at: https://www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx. Accessed on July 6, 2020.
419. Spiekerkoetter U, Lindner M, Santer R, et al. Treatment recommendations in long-chain fatty acid oxidation defects: consensus from a workshop. *J Inherit Metab Dis*. 2009;32(4):498-505.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/22/2020
Selected Revision	**Long-Chain Fatty Acid Oxidation Disorders:** Criteria were added requiring that the patient meet one of the following: inadequate efficacy or significant intolerance to over-the-counter (nutraceutical) medium-chain triglyceride supplements; a history of at least one severe or recurrent manifestation of long-chain fatty acid oxidation disorders; or currently receiving Dojolvi.	11/11/2020

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Imcivree Prior Authorization Policy

- Imcivree™ (setmelanotide subcutaneous injection – Rhythm Pharmaceuticals)

REVIEW DATE: 01/06/2021; selected revision 01/20/2021

OVERVIEW

Imcivree, a melanocortin 4 receptor agonist, is indicated for chronic weight management in patients ≥ 6 years of age with **obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency**, confirmed by genetic testing demonstrating variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance.[1]

As a limitation of use, Imcivree is not indicated for obesity due to suspected POMC, PCSK1, or LEPR deficiency with *POMC*, *PCSK1*, or *LEPR* variants classified as benign or likely benign.[1] Imcivree is also not indicated for obesity not related to POMC, PCSK1, or LEPR deficiency, including obesity associated with other genetic syndromes and general (polygenic) obesity.

Weight loss should be evaluated after 12 to 16 weeks of Imcivree treatment.[1] If a patient has not lost at least 5% of baseline body weight, or 5% of baseline body mass index for a patient with continued growth potential, Imcivree should be discontinued as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

Disease Overview

Monogenic obesity is a rare and severe early-onset form of obesity.[2] Unlike general obesity, environmental factors are much less impactful on obesity development in these patients. Fewer than 50 patients worldwide have been identified with POMC deficiency (*POMC* or *PCSK1* mutations); the prevalence of LEPR deficiency is unknown but is expected to account less than 3% of severe early-onset obesity. The true prevalence of these disorders is unknown and likely underestimated due to lack of provider awareness and genetic testing.[3] Clinical presentation is mainly characterized by major hyperphagia and ravenous hunger.[2] Patients with these disorders experience very rapid and early increase in weight, occurring within the first few days of life to early childhood. Lifestyle interventions may provide initial weight loss but are very difficult to maintain long-term in this population due to constant, insatiable hunger.[4] Isolated case reports of bariatric surgery have demonstrated some efficacy but are generally regarded as

disappointing relative to the general population, likely related to the underlying energy imbalance. Caution is urged before considering bariatric surgery in patients with monogenic obesity disorders.

In the pivotal trial for Imcivree, eligible patients were ≥ 6 years of age with obesity due to POMC deficiency (homozygous or compound heterozygous variants in *POMC* or *PCSK1*) or LEPR deficiency (homozygous or compound heterozygous variants in *LEPR*).[3] For patients 6 to < 18 years of age, obesity was defined as bodyweight > 95th percentile for age on growth chart assessment. For patients ≥ 18 years of age, obesity was defined as a BMI ≥ 30 kg/m^2.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Imcivree. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Imcivree as well as the monitoring required for adverse events and long-term efficacy, approval requires Imcivree to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Imcivree is recommended in those who meet the following criteria:

FDA-Approved Indications

123. Obesity Due to Proopiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency. Approve for the duration noted if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets the following criteria (i, ii, iii, and iv):
- **i.** Patient is ≥ 6 years of age; AND
- **ii.** Patient meets both of the following criteria (a and b):
  - **a)** Genetic testing demonstrates homozygous or compound heterozygous mutations in one of the following genes: *POMC*, *PCSK1*, or *LEPR*; AND
  - **b)** The genetic variant is interpreted as pathogenic, likely pathogenic, or of uncertain significance; AND
- **iii.** Patient meets one of the following criteria (a or b):
  - **a)** Patient is ≥ 18 years of age: Patient currently has a body mass index (BMI) ≥ 30 kg/m^2; OR
  - **b)** Patient is 6 to 17 years of age: Patient currently has a BMI ≥ 95th percentile for age and sex; AND
- **iv.** Imcivree is prescribed by or in consultation with an endocrinologist, a geneticist, or a physician who specializes in metabolic disorders.

B) Patient is currently receiving Imcivree. Approve for 1 year if the patient meets the following criteria:

(Note: For patients who have not completed at least 4 months of Imcivree therapy, refer to Initial Therapy criteria).
- **i.** Patient is ≥ 6 years of age; AND
- **ii.** Patient meets both of the following criteria (a and b):
  - **a)** Genetic testing demonstrates homozygous or compound heterozygous mutations in one of the following genes: *POMC*, *PCSK1*, or *LEPR*; AND
  - **b)** The genetic variant is interpreted as pathogenic, likely pathogenic, or of uncertain significance; AND
- **iii.** Patient meets one of the following criteria (a or b):
  - **a)** Patient has lost ≥ 5% of baseline body weight since initiating Imcivree therapy; OR

b) Patient meets both of the following (1 and 2):
(1) Patient has continued growth potential; AND
(2) Patient has lost ≥ 5% of baseline BMI since initiating Imcivree therapy; AND

iv. Imcivree is prescribed by or in consultation with an endocrinologist, a geneticist, or a physician who specializes in metabolic disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Imcivree is not recommended in the following situations:

132. Other Genetic Obesity Syndromes. (Note: Examples of genetic obesity syndromes include Prader-Willi syndrome, Bardet-Biedl syndrome, and Alström syndrome). Imcivree is not indicated for genetic obesity syndromes other than POMC-, PCSK1-, or LEPR-deficient obesity. Studies are currently underway in Bardet-Biedl and Alström syndromes.[5]

133. General Obesity. Imcivree is not indicated in this setting and there are no clinical data to support its use.[1]

134. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

192. Imcivree™ subcutaneous injection [prescribing information]. Boston, MA: Rhythm Pharmaceuticals; November 2020.
193. Huvenne H, Dubern B, Clément K, Poitou C. Rare genetic forms of obesity: clinical approach and current treatments in 2016. *Obes Facts*. 2016;9(3):158-73.
194. Clément K, van den Akker E, Argente J, et al; setmelanotide POMC and LEPR Phase 3 Trial Investigators. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. *Lancet Diabetes Endocrinol*. 2020 Dec;8(12):960-970.
195. Poitou C, Mosbah H, Clément K. Mechanisms in endocrinology: update on treatments for patients with genetic obesity. *Eur J Endocrinol*. 2020 Nov;183(5):R149-R166.
196. Rhythm Pharmaceuticals. Our Pipeline. Available at: https://www.rhythmtx.com/our-pipeline/. Accessed on January 4, 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/06/2021
Selected Revision	**Obesity Due to Proopiomelanocortin (POMC), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), or Leptin Receptor (LEPR) Deficiency:** Geneticist was added to the list of prescribing or consulting specialists.	01/20/2021

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Nitisinone Products

- Orfadin (nitisinone capsules and suspension – Sobi, Inc., generic [capsules only])
- Nityr (nitisinone tablets – Cycle Pharmacetuicals)

REVIEW DATE: 11/04/2020

OVERVIEW

Nitisinone products are hydroxy-phenylpyruvate dioxygenase inhibitors indicated for the treatment of adult and pediatric patients with **hereditary tyrosinemia type 1** in combination with dietary restriction of tyrosine and phenylalanine.[1-2]

Disease Overview

Hereditary tyrosinemia type 1 is a genetic disorder characterized by elevated blood levels of the amino acid tyrosine.[3-4] It is caused by mutations in the *FAH* gene, which lead to a deficiency of the enzyme fumarylacetoacetate hydrolase that is required for the breakdown of tyrosine. Symptoms usually appear in the first few months after birth and include failure to thrive, diarrhea, vomiting, jaundice, cabbage-like odor, and increased tendency to bleed. Diagnosis is most often via newborn screening (i.e., elevated alpha-fetoprotein and succinylacetone); however, carrier genetic testing and prenatal diagnosis by detection of succinylacetone in the amniotic fluid is also possible. Treatment should be immediately upon diagnosis with a diet restricted in tyrosine and phenylalanine and with nitisinone, which blocks the second step in the tyrosine degradation pathway.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of nitisinone products. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with nitisinone products as well as the monitoring required for adverse events and long-term efficacy, approval requires the agent to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of nitisinone products is recommended in those who meet the following criteria:

FDA-Approved Indications

124. Hereditary Tyrosinemia Type 1. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):

- **A)** According to the prescriber, diagnosis is supported by one of the following (i or ii):
  - **i.** Genetic testing confirmed a mutation of the *FAH* gene; OR
  - **ii.** Patient has elevated serum levels of alpha-fetoprotein (AFP) and succinylacetone; AND
- **B)** The medication is prescribed in conjunction with a tyrosine- and phenylalanine-restricted diet; AND
- **C)** Patient will not be taking the requested agent concurrently with another nitisinone product.
  Note: Examples of nitisinone products include Orfadin, generic nitisinone capsules, and Nityr. Concurrent use of these agents is not allowed; AND
- **D)** The medication is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of nitisinone products is not recommended in the following situations:

135. Concomitant Therapy with Nitisinone Products. Note: For example, concomitant use of Orfadin, generic nitisinone capsules, and/or Nityr. There are no data available to support concomitant use.

136. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

420. Orfadin [prescribing information]. Waltham, MA: Sobi, Inc.; May 2019.
421. Nityr [prescribing information]. Cambridge, UK: Cycle Pharmaceuticals; September 2020.
422. Genetic and Rare Diseases Information Center; National Institutes of Health, US Department of Health and Human Services [Web site]. Tyrosinemia type 1. Updated on: December 21, 2017. Accessed on October 2, 2019. Available at: https://rarediseases.info.nih.gov/diseases/2658/tyrosinemia-type-1.
423. National Organization for Rare Disorders. Tyrosinemia type 1. Accessed on October 2, 2019. Available at: https://rarediseases.org/rare-diseases/tyrosinemia-type-1/.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	03/13/2019
Early Annual Revision	The inclusion of generic nitisinone capsules was added to the policy. For Hereditary Tyrosinemia Type 1 indication, generic nitisinone capsules was added to criterion C within the examples of nitisinone products. For the condition of Concomitant Therapy with Nitisinone Products not recommended for approval, generic nitisinone capsules was added to the examples of nitisinone products.	10/09/2019
Annual Revision	No criteria changes.	11/04/2020

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Oxlumo Prior Authorization Policy

- Oxlumo™ (lumasiran injection for subcutaneous use – Alnylam Pharmaceuticals)

REVIEW DATE: 12/16/2020

OVERVIEW

Oxlumo is a hydroxyacid oxidase 1 (*HAO1*)-directed small interfering RNA indicated for the treatment of **primary hyperoxaluria type 1** to lower urinary oxalate levels in pediatric and adult patients.[1]

Disease Overview

Primary hyperoxaluria type 1 is a rare autosomal recessive inborn error of glyoxylate metabolism that results in the overproduction of oxalate, which forms insoluble calcium oxalate crystals that accumulate in the kidney and other organs.[4] Mutations in the alanine:glyoxylate aminotransferase gene (AGXT) cause primary hyperoxaluria type 1.[5] European studies estimate the prevalence of primary hyperoxaluria type 1 to be 1 to 3 cases per 1 million individuals in the population.[3]

Clinical Efficacy

The efficacy of Oxlumo for the treatment of primary hyperoxaluria type 1 was established in two pivotal studies.[1-3] One randomized, double-blind study included patients ≥ 6 years of age with confirmed AGXT mutations and urinary oxalate excretion ≥ 0.7 mmol/24 hr/1.73 m^2.[2] The least squares mean percent change from baseline to Month 6 (averaged over Months 3 through 6) in the 24-hour urinary oxalate corrected for body surface area was significantly reduced with Oxlumo compared with placebo.[1,2] By Month 6, 52% of Oxlumo-treated patients achieved a normal 24-hour urinary oxalate corrected for body surface area (BSA) compared with 0 placebo-treated patients. A second, single-arm study included patients < 6 years of age with a genetically-confirmed primary hyperoxaluria type 1 diagnosis and an elevated spot urinary oxalate:creatinine ratio for age/weight.[3] Oxlumo-treated patients achieved a 71% reduction from baseline to Month 6 (averaged over Months 3 through 6) in the spot urinary oxalate:creatinine ratio.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Oxlumo. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Oxlumo as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Oxlumo to be prescribed by or in consultation with a physician who specializes in the condition being treated. All reviews will be forwarded to the Medical Director for evaluation.

Documentation: Documentation is required for use of Oxlumo as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information. Subsequent coverage reviews for a patient who has previously met the documentation requirements and related criteria in the *Oxlumo Prior Authorization Policy* through the Coverage Review Department, and who is requesting reauthorization, the criteria utilized do NOT require re-submission of documentation for reauthorization, except for the criterion requiring documentation of a continued benefit from Oxlumo therapy.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Oxlumo is recommended in those who meet the following criteria:

FDA-Approved Indications

125. Primary Hyperoxaluria Type 1. Approve Oxlumo for the duration noted if the patient meets one of the following criteria (A or B):

- **A)** Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, and iv):
  - **i.** Patient has had a genetic test confirming the diagnosis of Primary Hyperoxaluria Type 1 via identification of an alanine:glyoxylate aminotransferase gene (AGXT) mutation **[documentation required]**; AND
  - **ii.** Patient has elevated urine oxalate excretion as demonstrated by ONE of the following (a or b):
    - **a)** Patient has a urinary oxalate excretion ≥ 0.7 mmol/24 hours/1.73 meters^2 **[documentation required]**; OR
    - **b)** Patient has a urinary oxalate:creatinine ratio above the age-specific upper limit of normal **[documentation required]**; AND
  - **iii.** Patient has not previously received a liver transplant for Primary Hyperoxaluria Type 1; AND
  - **iv.** The medication is prescribed by or in consultation with a nephrologist or urologist.
- **B)** Patient is Currently Receiving Oxlumo. Approve for 1 year if, according to the prescriber, the patient is continuing to derive benefit from Oxlumo as determined by the most recent (i.e., within the past 6 months) objective measurement **[documentation required]**.
  Note: Examples of objective measurements of a response to Oxlumo therapy are reduced urinary oxalate excretion, decreased urinary oxalate:creatinine ratio, or reduced plasma oxalate levels from baseline (i.e., prior to Oxlumo therapy) or improved or stabilized clinical signs/symptoms of Primary Hyperoxaluria Type 1 (e.g., nephrocalcinosis, formation of renal stones, renal impairment).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Oxlumo is not recommended in the following situations:

137. Primary Hyperoxaluria Type 2 (PH2). Oxlumo is not expected to be effective for the treatment of PH2, because its mechanism of action does not affect the metabolic pathways causing hyperoxaluria in PH2.[1] Oxlumo has not been studied for the treatment of patients with PH2.

138. Primary Hyperoxaluria Type 3 (PH3). Oxlumo is not expected to be effective for the treatment of PH3, because its mechanism of action does not affect the metabolic pathways causing hyperoxaluria in PH3.[1] Oxlumo has not been studied for the treatment of patients with PH3.

139. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

424. Oxlumo™ injection for subcutaneous use [prescribing information]. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; November 2020.
425. Garrelfs SF, Frishberg Y, Hulton SA, et al. ILLUMINATE-A, a phase III study of lumasiran, an investigational RNAi therapeutic, in children and adults with primary hyperoxaluria type 1 (PH1) [presentation LB002]. Presented at: the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) International Congress; virtual meeting; June 6-9, 2020.
426. Deschenes G, Cochat P, Magen D, et al. ILLUMINATE-B, a phase 3 open-label study to evaluate lumasiran, an RNAi therapeutic, in young children with primary hyperoxaluria type 1 (PH1) [presentation PO1624]. Presented at: the American Society of Nephrology (ASN) Kidney Week; virtual meeting; October 22-25, 2020.
427. Milliner DS, Harris PC, Cogal AG, et al. Primary Hyperoxaluria Type 1. Gene Reviews® Available at: https://www.ncbi.nlm.nih.gov/books/NBK1283/. Updated November 30, 2017. Accessed on December 2, 2020.
428. Primary Hyperoxaluria: MedlinePlus Genetics. U.S. National Library of Medicine; National Institutes of Health; Department of Health and Human Services. Available at: https://medlineplus.gov/genetics/condition/primary-hyperoxaluria/#resources. Accessed on December 2, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Phenylbutyrate Products

- Buphenyl (sodium phenylbutyrate tablets and powder for oral solution – Horizon Pharma, generics)
- Ravicti (glycerol phenylbutyrate oral liquid – Horizon Pharma)

DATE REVIEWED: 03/11/2020

OVERVIEW

Buphenyl is indicated as adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase, or argininosuccinic acid synthetase.[1] It is indicated in all patients with neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first 28 days of life). It is also indicated in patients with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy. Early diagnosis is important so that treatment is initiated early for improved survival. Any episode of acute hyperammonemia should be treated as a life-threatening emergency. Buphenyl must be combined with dietary protein restriction and, in some cases, essential amino acid supplementation. Of note, Buphenyl tablet/powder contains 124 mg of sodium per gram of sodium phenylbutyrate (12.4% w/w) or about 2.5 grams of sodium in 40 tablets; safety or efficacy data unavailable for > 40 tablets/day. Therefore, it should be used with great care, if at all, in patients with congestive heart failure or severe renal insufficiency, and in clinical states in which there is sodium retention with edema.

Ravicti is indicated for use as a nitrogen-binding agent for chronic management patients with urea cycle disorders that cannot be managed by dietary protein restriction and/or amino acid supplementation alone.[2] Ravicti must be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements). Ravicti is not indicated for the treatment of acute hyperammonemia in patients with urea cycle disorders. Safety and efficacy for the treatment of N-acetyl glutamate synthase (NAGS) deficiency have not been established.

Disease Overview

Urea cycle disorders are rare inborn errors of metabolism which result from mutations in the genes encoding for one of the six enzymes necessary for normal function of the urea cycle: arginase, citrullinemia, arginosuccinic acid synthetase, N-acetyl glutamate synthetase, ornithine transcarbamylase, and carbamyl phosphate synthetase.[3-4] They lead to increased amounts of ammonia in the blood which may cause disturbed brain function and severe brain damage. Signs of disease include decreased mental awareness, vomiting, combativeness, slurred speech, unstable gait, and unconsciousness. Diagnosis begins with a clinical suspicion of hyperammonemia.[6] Typically, patients have normal glucose and electrolyte levels. Enzymatic diagnosis and/or genetic testing is also available; however, treatment should not be delayed while waiting for a final diagnosis. Most deaths have occurred during an episode of acute hyperammonemic encephalopathy.[3-4] Treatment includes use of alternative waste nitrogen excretion pathways (e.g., Buphenyl, Ravicti); other treatments may include hemodialysis, dietary protein restriction, and, in some cases, essential amino acid supplementation.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Phenylbutyrate Products (Buphenyl, Ravicti). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Phenylbutyrate Products (Buphenyl, Ravicti) as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Phenylbutyrate Products (Buphenyl, Ravicti) is recommended in those who meet the following criteria:

FDA-Approved Indications

126. Urea Cycle Disorders (Note: Examples include deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase, or argininosuccinic acid synthetase). Approve for the duration noted if the patient meets ALL of the following (A, B, C, and D):

- **A)** According to the prescriber, the diagnosis was confirmed by one of the following (i or ii):
  - **i.** Approve for 1 year if genetic testing confirmed a mutation resulting in a urea cycle disorder; OR
  - **ii.** Approve for 3 months if the patient has hyperammonemia diagnosed with an ammonia level above the upper limit of the normal reference range for the reporting laboratory.
    Note: Reference ranges are dependent upon patient's age; AND
- **B)** The medication is prescribed in conjunction with a protein-restricted diet; AND
- **C)** The patient will not be taking Buphenyl and Ravicti concurrently; AND
- **D)** The medication is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Phenylbutyrate Products (Buphenyl, Ravicti) have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

140. Concomitant Therapy with Buphenyl and Ravicti. There are no data available to support concomitant use.

141. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

429. Buphenyl [prescribing information]. Lake Forest, IL: Horizon Pharma; November 2018.
430. Ravicti [prescribing information]. Lake Forest, IL: Horizon Pharma; October 2019.
431. Diaz GA, Krivitzky LS, Mokhtarani M, et al. Ammonia control and neurocognitive outcome among urea cycle disorder patients treated with glycerol phenylbutyrate. *Hepatology*. 2013;57(6):2171-2179.
432. Hereditary urea cycle abnormality. Medline Plus. A service of the U.S. National Library of Science, National Instituties of Health (NIH). Updated February 13, 2020. Available at: http://www.nlm.nih.gov/medlineplus/ency/article/000372.htm. Accessed on February 25, 2020.
433. Summar M. Urea cycle disorders. National Organization of Rare Disorders [Web site]. Available at: https://rarediseases.org/physician-guide/urea-cycle-disorders/. Accessed on February 25, 2020.
434. National Organization for Rare Disorders (NORD). Urea cycle disorders. Accessed on February 25, 2020. Available at: https://rarediseases.org/physician-guide/urea-cycle-disorders/.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	03/13/2019
Annual revision	**Urea Cycle Disorders:** For criterion that approves if the patient has hyperammonemia, clarify that this is according to laboratory testing.	03/11/2020

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Tiopronin Products Prior Authorization Policy

- Thiola® (tiopronin tablets – Mission Pharmacal)
- Thiola® EC (tiopronin delayed-release tablets – Mission Pharmacal)

REVIEW DATE: 09/16/2020

OVERVIEW

Thiola and Thiola EC are indicated, in combination with high fluid intake, alkali, and diet modification, for the prevention of cystine kidney stone formation in adults and pediatric patients ≥ 20 kg with severe homozygous cystinuria, who are not responsive to these measures alone.[1,2]

Disease Overview

Cystinuria is an autosomal recessive disorder of abnormal cystine transport.[3] The estimated prevalence is 1:7,000 to 1:10,000 individuals in the US. Excessive undissolved cystine in the urine leads to formation of stones in the kidney, bladder, and/or ureter. Symptoms typically begin to manifest between 10 and 30 years of age, although elevated cystine excretion may be found in infancy. Diagnosis is made clinically based on quantitative urinary cystine assays; genetic testing is not routine as it does not change medical management.[4] Homozygotes exhibit urinary cystine excretion > 300 to 400 mg/L/day, whereas heterozygotes have intermediate urinary cystine excretion. Treatment is directed at decreasing urinary cystine concentration (generally targeting a urine cystine < 250 mg/L) and enhancing solubility.[4,5] Tiopronin products work by binding to cystine and increasing urinary solubility.[4]

Guidelines

According to the American Urological Association guideline for medical management of kidney stones (2014), all patients with cystine kidney stones should be encouraged to drink large amounts of fluid to maintain low urinary cystine concentrations; often volumes of 4 liters per day are required.[5] Recommended dietary modifications include restriction of sodium and animal proteins. Alkalization of urine is also used to improve cystine solubility. This can be achieved through increased fruit and vegetable intake and/or with medications such as potassium citrate. The guideline recommends tiopronin for patients with cystine kidney stones who are unresponsive to increased fluid intake, dietary modification, and urinary alkalization.

Captopril, another thiol agent, has not been shown to be effective for the prevention of recurrent cystine stones. D-penicillamine may be associated with more adverse events and is not preferred.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of tiopronin products (Thiola, Thiola EC). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with tiopronin products, approval requires the requested medication to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Thiola or Thiola EC is recommended in those who meet the following criteria:

FDA-Approved Indications

25. Cystinuria. Approve for 1 year if the patient meets the following criteria (A, B, and C):

- **E)** Diagnosis of cystinuria has been confirmed based on laboratory testing (e.g., urinary cystine crystals present on microscopy, quantitative urine cystine assay); AND
- **F)** According to the prescriber, the patient has had an inadequate response to high fluid intake, dietary modification, and urinary alkalization; AND
- **G)** The medication is prescribed by, or in consultation with, a nephrologist, urologist, or physician who specializes in the treatment of cystinuria.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Thiola or Thiola EC is not recommended in the following situations:

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

188. Thiola® [prescribing information]. San Antonio, TX: Mission Pharmacal; June 2019.
189. Thiola® EC [prescribing information]. San Antonio, TX: Mission Pharmacal; June 2019.
190. Cystinuria. National Organization for Rare Disorders. Updated 2020. Available at: https://rarediseases.org/rare-diseases/cystinuria/. Accessed on September 9, 2020.
191. Castro Pereira DJ, Schoolwerth AC, Pais VM. Cystinuria: current concepts and future directions. *Clin Nephrology.* 2015;83(3):138-146.
192. Pearle MS, Goldfarb DS, Assimos DG, et al.; American Urological Association. Medical management of kidney stones: AUA guideline. *J Urol.* 2014;192(2):316-24. Available at: https://www.auajournals.org/doi/10.1016/j.juro.2014.05.006. Accessed on September 9, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	09/18/2019
Annual Revision	No changes to criteria.	09/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Xuriden Prior Authorization Policy
- Xuriden® (uridine triacetate oral granules – Wellstat Therapeutics)

REVIEW DATE: 07/29/2020

OVERVIEW
Xuriden, a pyrimidine analog for uridine replacement, is indicated for the treatment of hereditary orotic aciduria.[1] Xuriden is supplied as oral granules in a 2 gram packet. The recommended starting dose is 60 mg/kg once daily, which may be increased to 120 mg/kg (not to exceed 8 grams) once daily for insufficient efficacy. Any unused portion of a packet must be discarded; it should not be saved for subsequent doses.

Disease Overview
Hereditary orotic aciduria, also known as orotic aciduria type 1, is an extremely rare, autosomal recessive genetic disorder estimated to affect less than 1:1,000,000 live births.[1-3] Only about 20 cases have been reported in the medical literature.[2] In hereditary orotic aciduria, mutation in the *UMPS* gene leads to defective uridine 5'monophosphate synthase.[1,2] Deficiency in this enzyme prevents the last two steps in pyrimidine biosynthesis, leading to inadequate levels of uridine monophosphate and excess levels of orotic acid (a uridine precursor). Because the condition is so rare, hereditary orotic aciduria is not fully understood. Affected infants may develop megaloblastic anemia, developmental delays, or failure to thrive. Orotic acid crystals in the urine can lead to urinary obstruction. Xuriden replaces uridine in the circulation, and as a result of feedback inhibition, overproduction of orotic acid is reduced. Diagnosis is made by detailed patient and family history as well as thorough clinical evaluation and examination of urine. Most individuals have their diagnosis confirmed through molecular genetic testing; however, this is only available at specialized laboratories.

POLICY STATEMENT
Prior authorization is recommended for prescription benefit coverage of Xuriden. Because of the specialized skills required for evaluation and diagnosis of patients treated with Xuriden, approval requires the requested medication to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Xuriden is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Hereditary Orotic Aciduria (Orotic Aciduria Type 1).** Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient has hereditary orotic aciduria confirmed by at least one of the following (i or ii):
     - **i.** Molecular genetic testing confirming mutation in the *UMPS* gene; OR
     - **ii.** Clinical diagnosis supported by both of the following (a and b):
       - **a)** First-degree family relative (i.e., parent or sibling) with hereditary orotic aciduria; AND

b) Urinary orotic acid level above the normal reference range for the reporting laboratory; AND

B) Xuriden is prescribed by, or in consultation with, a metabolic specialist, geneticist, or physician specializing in the condition being treated.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xuriden is not recommended in the following situations:

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

193. Xuriden® oral granules [prescribing information]. Rockville, MD: Wellstat Therapeutics; December 2019.
194. Hereditary orotic aciduria. National Organization for Rare Disorders. Updated 2018. Available at: https://rarediseases.org/rare-diseases/hereditary-orotic-aciduria/. Accessed on July 22, 2020.
195. Orotic aciduria type 1. Genetic and Rare Diseases Information Center. Updated September 13, 2017. Available at: https://rarediseases.info.nih.gov/diseases/5429/orotic-aciduria-type-1. Accessed on July 22, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New policy	--	08/07/2019
Annual revision	No changes to criteria.	07/29/2020

PRIOR AUTHORIZATION POLICY

POLICY: Methergine® (methylergonovine maleate tablets, USP – Lupin Pharma, generics)

DATE REVIEWED: 05/27/2020

OVERVIEW

Methylergonovine is a semi-synthetic ergot alkaloid used for the prevention and control of postpartum hemorrhage.[1] Methylergonovine is indicated for management of uterine atony, hemorrhage and subinvolution of the uterus following delivery of the placenta.

The National Headache Foundation notes that methylergonovine can cause constriction of the smooth muscles in the blood vessels and this effect can be helpful in treating vascular headaches, such as migraines.[2] Although methylergonovine is more commonly used for prevention of migraine headaches, it can be taken for acute attacks. However, methylergonovine should only be used for limited periods of time in most patients and only under careful supervision of a physician. The dose of methylergonovine used for migraines is 0.2 to 0.4 mg three times a day; a maximum dose of 1.6 mg/day has been reported (eight 0.2 mg tablets per day).[3]

Disease Overview, Migraine

Migraine, a chronic neurologic disease, is characterized by attacks of throbbing headache with sensitivities to light and sound.[4] The treatment of migraines is individualized and choice of therapy is based on many factors, including: patient preference; severity and frequency of attacks; the presence, type, and severity of associated symptoms; treatment response to prior therapies; presence of comorbid and coexistent illness; contraindications (e.g., cardiovascular disease); and use of concomitant medications.

Guidelines/Recommendations

An updated assessment of the preventive and acute treatment of migraine by the American Headache Society (2018) reaffirms previous migraine guidelines. The current update lists the triptans and dihydroergotamine (DHE) as effective treatments for moderate or severe acute migraine attacks and mild to moderate attacks that respond poorly to nonsteroidal anti-inflammatory drugs (NSAIDs) or caffeinated combinations (e.g., aspirin + acetaminophen + caffeine). Opioid medications are probably effective; however, they are not recommended for regular use. The recommendation remains that clinicians must consider medication efficacy, potential side effects, and potential medication-related adverse events when prescribing acute medications for migraines. Treatment at the first sign of pain improves the probability of achieving freedom from pain and reduces attack-related disability. Migraine patients who need to use acute treatments on a regular basis should limit treatment to an average of two headache days per week, and patients who exceed this limit should be offered preventive treatment. Therapies that are used for migraine prevention include antiepileptics (divalproex sodium, valproate sodium, topiramate), beta-blockers (metoprolol, propranolol, timolol), onabotulinumtoxin A, and frovatriptan (for short-term preventive treatment of menstrual migraine).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of methylergonovine prescriptions with quantities exceeding 28 tablets per 30 days. Twenty-eight (28) tablets per month will be sufficient to treat uterine atony, hemorrhage and subinvolution of the uterus following the delivery of the placenta (FDA-approved indication). Because of the specialized skills required for evaluation and diagnosis of patients with migraines who are treated with methylergonovine as well as the monitoring required for adverse events and long-term efficacy, approval requires methylergonovine to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 1 year in duration unless otherwise noted below.

Automation: Methylergonovine prescriptions for 28 tablets (0.2 mg strength) per 30 days are excluded from Prior Authorization (PA). The PA policy will only apply to methylergonovine prescriptions with quantities exceeding 28 tablets per 30 days.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of methylergonovine is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Uterine Atony, Hemorrhage and Subinvolution of the Uterus.** Do not approve. The initial quantity of 28 tablets is sufficient to treat this condition; quantities > 28 tablets for this indication will not be approved.

Other Uses with Supportive Evidence

2. **Migraine Headaches (Acute Treatment).** Approve methylergonovine for 1 year if the patient meets ONE of the following criteria (A or B):
   - **F)** Patient is already receiving methylergonovine therapy; OR
   - **G)** The patient meets all of the following criteria (i, ii, and iii):
     - **i.** Patient has tried and had inadequate efficacy and/or unacceptable side effects to at least one triptan therapy.

Note: Examples of triptans: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan); AND

ii. Patient has tried and had inadequate efficacy and/or unacceptable side effects to at least one other type of abortive therapy.

Note: Examples of abortive therapies include analgesics [acetaminophen, nonsteroidal anti-inflammatories {NSAIDs}], butalbital-containing products [butalbital-acetaminophen, butalbital-acetaminophen-caffeine, butalbital-acetaminophen-caffeine-codeine, butalbital-aspirin-caffeine, butalbital-aspirin-caffeine-codeine], dihydroergotamine [DHE, Migranal®, generics]); AND

iii. The medication is prescribed by, or in consultation with, a neurologist or headache specialist.

3. **Migraine Headaches (Prophylaxis).** Approve methylergonovine for 1 year if the patient meets both of the following criteria (A and B):

A) Patient has tried at least two other prophylactic pharmacologic therapies, each from a different pharmacologic class.

Note: Examples of prophylactic pharmacologic therapies include angiotensin receptor blocker [e.g., candesartan], angiotensin converting enzyme inhibitor [e.g., lisinopril], anticonvulsant [e.g., divalproex sodium, sodium valproate, topiramate], beta-blocker [e.g., atenolol, metoprolol, nadolol, propranolol, timolol], calcium channel blocker [e.g., diltiazem, verapamil], tricyclic antidepressant [e.g., amitriptyline], other antidepressant [e.g., venlafaxine]); AND

B) The medication is prescribed by, or in consultation with, a neurologist or headache specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Methylergonovine has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below.

148. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Methergine® [prescribing information]. Baltimore, MD: Lupin Pharma; January 2016.
2. Methergine, National Headache Foundation. Available at: http://www.headaches.org/2007/10/25/methergine/. Accessed on May 22, 2019.
3. Saper JR, Evans RW. Oral methylergonovine maleate for refractory migraine and cluster headache prevention. *Headache.* 2013 Feb;53(2):378-81
4. American Headache Society. The American Headache Society position statement on integrating new migraine treatments into clinical practice. *Headache*. 2019;59:1-18

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	05/30/2018
Annual revision	No criteria changes.	05/29/2019
Annual revision	No criteria changes. Formatting: Revised the list of triptans, abortive therapies, and prophylactic pharmacologic therapies to Notes.	05/27/2020

PRIOR AUTHORIZATION POLICY

POLICY: Migraine – Nurtec™ ODT (rimegepant sulfate orally disintegrating tablet – Biohaven)

DATE REVIEWED: 03/04/2020; selected revision 06/03/2020

OVERVIEW

Nurtec ODT is indicated for the acute treatment of migraine with or without aura in adults.[1] Limitations of Use: Nurtec ODT is not indicated for the prevention of migraine. The recommended dose of Nurtec ODT is 75 mg taken orally. The maximum dose is 75 mg in a 24 hour period. The safety of treating more than 15 migraines in a 30 day period has not been established.

Disease Overview

Migraine is a common, ongoing condition marked by paroxysmal, unilateral attacks of moderate to severe throbbing headache which is aggravated by routine physical activity (e.g., walking or climbing stairs) and associated with nausea, vomiting, and/or photophobia and phonophobia.[2] Migraine headache episodes typically last 4 to 72 hours, if untreated. Migraine affects approximately 15% of US adults.[3] Migraines have been defined as chronic or episodic. Chronic migraine is described by the International Headache Society as headache occurring on ≥ 15 days/month for more than 3 months, which has the features of migraine headache on ≥ 8 days/month.[2] Episodic migraine is characterized by headaches that occur < 15 days/month.[4] Patients with episodic migraine may transform to chronic migraine over time at a rate of about 2.5% of patients per year. Potential strategies for preventing migraine transformation include preventing and treating headaches, lifestyle modifications, or effective management of comorbidities (e.g., obesity, obstructive sleep apnea, depression, anxiety). Episodic migraine is more common than chronic migraine; however, chronic migraine is associated with a markedly greater personal and societal burden.

Triptans (e.g., almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) are considered the gold standard for acute treatment of moderate to severe migraine headaches or mild to moderate migraine headaches that respond poorly to over-the-counter (OTC) analgesics. An updated assessment of the **preventive and acute treatment of migraine by the American Headache Society** (2018) lists the triptans and dihydroergotamine as effective treatments for moderate or severe acute migraine attacks and mild to moderate attacks that respond poorly to nonsteroidal anti-inflammatory drugs (NSAIDs) or caffeinated combinations (e.g., aspirin + acetaminophen + caffeine).[5] Treat at the first sign of pain to improve the probability of achieving freedom from pain and reduce attack-related disability.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Nurtec ODT. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nurtec ODT is recommended in those who meet the following criteria:

FDA-Approved Indications

127. Migraine, Acute Treatment. Approve for 1 year if the patient meets the following criteria (A and B):

- **A)** The patient is ≥ 18 years of age; AND
- **B)** The patient meets ONE of the following (i or ii):
  - **i.** The patient has tried at least one triptan therapy; OR

ii. The patient has a contraindication to triptan(s) according to the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Nurtec ODT has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

142. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

435. Nurtec ODT [prescribing information]. New Haven, CT: Biohaven Pharmaceuticals; February 2020.
436. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629-808.
437. MacGregor EA. In the clinic. Migraine. *Ann Intern Med*. 2017;166(7):ITC49-ITC64.
438. Lipton RB, Silberstein SD. Episodic and chronic migraine headache: breaking down barriers to optimal treatment and prevention. *Headache*. 2015;52:103-122.
439. American Headache Society. The American Headache Society position statement on integrating new migraine treatments into clinical practice. *Headache*. 2019;59:1-18.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	03/04/2020
Selected revision	For the approval condition of Migraine, Acute Treatment, the number of triptans tried was changed from two to one.	06/03/2020

PRIOR AUTHORIZATION POLICY

POLICY: Migraine – Reyvow Prior Authorization Policy

- Reyvow™ (lasmiditan tablet – Lilly)

REVIEW DATE: 12/16/2020

OVERVIEW

Reyvow, a serotonin (5-HT) subtype 1F receptor agonist, is indicated for the **acute treatment of migraine** with or without aura in adults.[1] Limitations of Use: Reyvow is not indicated for the preventive treatment of migraine.

Reyvow is a first-in-class ditan that binds with high affinity and selectivity to the 5-HT_{1F} receptor.[1-4] Activation of this receptor does not constrict blood vessels. Migraine involves activation and sensitization of trigeminal nociceptors in the dura mater. Reyvow acts on the trigeminal system without causing vasoconstriction because of its low affinity for 5-HT_{1B} receptors. The recommended dose is 50 mg, 100 mg, or 200 mg as needed with or without food.[1] No more than one dose should be taken in 24 hours; a second dose has not been shown to be effective for the same migraine attack. Reyvow should not be taken unless the patient can wait at least 8 hours between dosing and driving or operating machinery. The safety of treating an average of more than four migraine attacks in a 30-day period has not been established.

Disease Overview

Migraine is a common, ongoing condition marked by paroxysmal, unilateral attacks of moderate to severe throbbing headache which is aggravated by routine physical activity (e.g., walking or climbing stairs) and associated with nausea, vomiting, and/or photophobia and phonophobia.[5] Migraines have been defined as chronic or episodic. Chronic migraine is described by the International Headache Society as headache occurring on ≥ 15 days/month for more than 3 months, which has the features of migraine headache on ≥ 8 days/month. Episodic migraine is characterized by

headaches that occur < 15 days/month.[6] Patients with episodic migraine may transform to chronic migraine over time. Potential strategies for preventing migraine transformation include preventing and treating headaches, lifestyle modifications, or effective management of comorbidities (e.g., obesity, obstructive sleep apnea, depression, anxiety). Episodic migraine is more common than chronic migraine; however, chronic migraine is associated with a markedly greater personal and societal burden.

Guidelines

Triptans (e.g., almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) are considered the gold standard for acute treatment of moderate to severe migraine headaches or mild to moderate migraine headaches that respond poorly to over-the-counter (OTC) analgesics. An updated assessment of the **preventive and acute treatment of migraine by the American Headache Society** (2018) lists the triptans and dihydroergotamine as effective treatments for moderate or severe acute migraine attacks and mild to moderate attacks that respond poorly to nonsteroidal anti-inflammatory drugs (NSAIDs) or caffeinated combinations (e.g., aspirin + acetaminophen + caffeine).[7] Treat at the first sign of pain to improve the probability of achieving freedom from pain and reduce attack-related disability.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Reyvow. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Reyvow is recommended in those who meet the following criteria:

FDA-Approved Indications

128. Migraine, Acute Treatment. Approve for 1 year if the patient meets the following criteria (A and B):

- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets ONE of the following (i or ii):
  - **i.** Patient has tried at least one triptan therapy; OR
  - **ii.** Patient has a contraindication to triptan(s) according to the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Reyvow is not recommended in the following situations:

143. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

440. Reyvow® tablets [prescribing information]. Indianapolis, IN: Lilly USA, LLC; July 2020.
441. Do TP, Guo S, Ashina M. Therapeutic novelties in migraine: new drugs, new hope? *J Headache Pain*. 2019;20(1):37.
442. Kuca B, Silberstein SD, Wietecha L, et al. Lasmiditan is an effective acute treatment for migraine. *Neurology*. 2018;91:e2222-e2232.
443. Goadsby PJ, Wietecha LA, Dennehy EB, et al. Phase 3 randomized, placebo-controlled, double-blind study of lasmiditan for acute treatment of migraine. *Brain*. 2019;142:1894-1904.
444. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition. *Cephalalgia*. 2018;38(1):1-211.
445. Lipton RB, Silberstein SD. Episodic and chronic migraine headache: breaking down barriers to optimal treatment and prevention. *Headache*. 2015;52:103-122.

446. American Headache Society. The American Headache Society position statement on integrating new migraine treatments into clinical practice. *Headache*. 2019;59:1-18.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/18/2019
Selected Revision	For the approval condition of Migraine, Acute Treatment, the number of triptans tried was changed from two to one.	06/03/2020
Annual Revision	No criteria changes.	12/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Migraine – Ubrelvy Prior Authorization Policy

- Ubrelvy™ (ubrogepant tablet – Allergan)

REVIEW DATE: 02/03/2021

OVERVIEW

Ubrelvy, a calcitonin gene-related peptide receptor antagonist, is indicated for the acute treatment of migraine headache with or without aura in adults.[1] Limitations of Use: Ubrelvy is not indicated for the preventive treatment of migraine.

Guidelines

Triptans (e.g., almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) are considered the gold standard for acute treatment of moderate to severe migraine headaches or mild to moderate migraine headaches that respond poorly to over-the-counter (OTC) analgesics.[2] An updated assessment of the **preventive and acute treatment of migraine by the American Headache Society** (2018) lists the triptans and dihydroergotamine as effective treatments for moderate or severe acute migraine attacks and mild to moderate attacks that respond poorly to nonsteroidal anti-inflammatory drugs (NSAIDs) or caffeinated combinations (e.g., aspirin + acetaminophen + caffeine).[3] Treat at the first sign of pain to improve the probability of achieving freedom from pain and reduce attack-related disability.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ubrelvy. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ubrelvy is recommended in those who meet the following criteria:

FDA-Approved Indications

129. Migraine, Acute Treatment. Approve for 1 year if the patient meets the following criteria (A and B):

- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets ONE of the following (i or ii):
  - **i.** Patient has tried at least one triptan therapy; OR
  - **ii.** Patient has a contraindication to triptan(s) according to the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ubrelvy is not recommended in the following situations:

144. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

447. Ubrelvy™ tablets [prescribing information]. Madison, NJ: Allergan; December 2019.
448. MacGregor EA. In the clinic. Migraine. *Ann Intern Med*. 2017;166(7):ITC49-ITC64.
449. American Headache Society. The American Headache Society position statement on integrating new migraine treatments into clinical practice. *Headache*. 2019;59:1-18.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/29/2020
Selected Revision	**Migraine, Acute Treatment**: The number of triptans tried was changed from two to one.	06/03/2020
Annual Revision	No criteria changes.	02/03/2021

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Ampyra Prior Authorization Policy

- Ampyra® (dalfampridine extended-release tablets – Acorda Therapeutics, generic)

REVIEW DATE: 10/14/2020

OVERVIEW

Ampyra is a potassium channel blocker that is indicated to improve walking in adults with multiple sclerosis (MS).[1] This was demonstrated by an increase in walking speed.

Safety

Ampyra is contraindicated in patients with a history of seizures; moderate or severe renal impairment (estimated creatinine clearance [CrCl] ≤ 50 mL/min); and in those with a history of hypersensitivity to Ampyra or 4-aminopyridine.[1]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ampyra. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ampyra as well as the monitoring required for adverse events and long-term efficacy, approval requires Ampyra to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ampyra is recommended in those who meet the following criteria:

FDA-Approved Indications

46. Multiple Sclerosis (MS). Approve for the duration noted below if the patient meets one of the following criteria (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets all of the following (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Ampyra is being used to improve or maintain mobility; AND
- **iii.** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR

B) Patient Currently Receiving Ampyra. Approve for 1 year of the patient meets all of the following (i, ii, iii, and iv):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Ampyra is being used to improve or maintain mobility; AND
- **iii.** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; AND
- **iv.** According to the prescriber the patient has responded to or is benefiting from therapy.
  Note: Examples of response or benefits include an increase in walking speed and/or improvement in strength, coordination, ambulation, or balance.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ampyra is not recommended in the following situations:

149. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

55. Ampyra® extended-release tablets [prescribing information]. Ardsley, NY: Acorda Therapeutics, Inc.; December 2019.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes	08/15/2018
Early Annual Revision	Generic Ampyra was added to the policy. The approval duration was changed from 3 years of 1 year.	10/03/2018
Annual Revision	No criteria changes.	10/02/2019
Annual Revision	**Multiple Sclerosis:** Criteria are now broken down into patients receiving initial therapy and patients currently receiving Ampyra. Regarding initial approval, criteria are now to approve for 4 months (previously, the duration of approval was 1 year). Criteria were added that the agent is approved if the patient is ≥ 18 years of age. Also, regarding the criterion that requires that the patient is using Ampyra to improve mobility (in a patient with multiple sclerosis), the wording "or maintain (mobility)" was added. The approval duration for patients currently receiving Ampyra continues to be 1 year. Criteria for patients receiving initial therapy and for patients currently receiving Ampyra are the same except for patients currently receiving Ampyra, the patient has to demonstrate response or benefit from therapy, according to the prescriber. A note was added that examples of response or benefits include an increase in walking speed and/or improvement in strength, coordination or balance.	10/14/2020

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Aubagio Prior Authorization Policy

- Aubagio® (teriflunomide tablets – Genzyme/Sanofi)

REVIEW DATE: 08/05/2020; selected revision 09/09/2020

OVERVIEW

Aubagio, a pyrimidine synthesis inhibitor, is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease, in adults.[1]

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[2] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[3] as well as in 2017.[4] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-4] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

Safety

Aubagio has a Boxed Warning regarding hepatotoxicity and the risk of embryofetal toxicity.[1]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Aubagio. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Aubagio as well as the monitoring required for adverse events and long-term efficacy, approval requires Aubagio to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Aubagio is recommended in those who meet the following criteria:

FDA-Approved Indication

1. Multiple Sclerosis. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient has a relapsing form of multiple sclerosis; AND
Note: Examples of relapsing forms of multiple sclerosis (MS) include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

B) Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Aubagio is not recommended in the following situations:

150. Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.
Note: Examples of disease modifying agents used for multiple sclerosis include Avonex® (interferon beta 1a injection [intramuscular]), Betaseron®/Extavia® (interferon beta-1b injection), Rebif® (interferon beta-1a injection [subcutaneous]), Copaxone®/Glatopa® (glatiramer acetate injection), Plegridy® (peginterferon beta-1a injection), Gilenya® (fingolimod tablets), Mavenclad® (cladribine tablets), Mayzent® (siponomid tablets), Tecfidera® (dimethyl fumarate delayed-release capsules), Bafiertam® (monomethyl fumarate delayed-release capsules), Vumerity® (diroximel fumarate delayed-release capsules), Zeposia® (ozanimod capsules), Ocrevus® (ocrelizumab injection for intravenous use), Tysabri® (natalizumab injection for intravenous infusion), Lemtrada® (alemtuzumab injection for intravenous use), and Kesimpta® (ofatumumab injection for subcutaneous use).[2] These agents are not indicated for use in combination. Additional data are required to determine if use of disease-modifying MS agents in combination is safe and provides added efficacy.

151. Non-Relapsing Forms of Multiple Sclerosis.
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis. The efficacy of Aubagio has not been established in patients with multiple sclerosis with non-relapsing forms of multiple sclerosis.[1]

152. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

196. Aubagio® tablets [prescribing information]. Cambridge, MA: Genzyme Corporation (a Sanofi company); February 2020.

197. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. September 2019. Available at: http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed on September 9, 2020.
198. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
199. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Zinbryta was removed from the market. Therefore, Zinbryta was deleted from the list of medications in which Aubagio should not be used with concomitantly.	08/15/2018
Annual Revision	The wording of "for PSM" was removed from the document title. The following criteria changes were made. **Multiple Sclerosis:** The examples of relapsing forms of MS were removed. **Conditions Not Recommended for Approval:** For patients with Non-Relapsing Forms of MS, the example of primary progressive MS is now listed as a note. Regarding Use with Other Disease-Modifying Agents for MS, the examples are now listed as a note with Mavenclad and Mayzent added as examples.	07/17/2019
Annual Revision	The following criteria changes were made: **Conditions Not Recommended for Approval:** Bafiertam, Vumerity, and Zeposia were added to the Note that provides examples of disease-modifying MS agents in which Aubagio should not be used with concurrently.	08/05/2020
Selected Revision	**Multiple Sclerosis:** Examples of relapsing forms of MS were added in a Note. **Conditions Not Recommended for Approval:** Regarding Use with Other Disease-Modifying Agents for MS, Kesimpta was added to the list of examples provided in the Note.	09/09/2020

PSM – Preferred Specialty Management; MS – Multiple sclerosis.

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Avonex Prior Authorization Policy

- Avonex® (interferon beta-1a injection for intramuscular use – Biogen)

REVIEW DATE: 08/05/2020; selected revision 09/09/2020

OVERVIEW

Avonex is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease in adults.[1]

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[2] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the

distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[3] as well as in 2017.[4] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-4] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Avonex. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Avonex as well as the monitoring required for adverse events and long-term efficacy, approval requires Avonex to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Avonex is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Multiple Sclerosis.** Approve for 3 years if the patient meets the following criteria (A and B):
   - **R)** Patient has a relapsing form of multiple sclerosis; AND
     Note: Examples of relapsing forms of multiple sclerosis (MS) include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
   - **S)** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Avonex is not recommended in the following situations:

22. **Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.**
    Note: Examples of disease modifying agents used for multiple sclerosis include Betaseron®/Extavia® (interferon beta-1b injection), Rebif® (interferon beta-1a injection [subcutaneous]), Copaxone®/Glatopa® (glatiramer acetate injection), Plegridy® (peginterferon beta-1a injection), Aubagio® (teriflunomide tablets), Gilenya® (fingolimod tablets), Mavenclad® (cladribine tablets), Mayzent® (siponimod tablets), Tecfidera® (dimethyl fumarate delayed-release capsules), Bafiertam® (monomethyl fumarate delayed-release capsules), Vumerity® (diroximel fumarate delayed-release capsules), Zeposia® (ozanimod capsules), Ocrevus® (ocrelizumab injection for intravenous use),

Tysabri® (natalizumab injection for intravenous infusion), Lemtrada® (alemtuzumab injection for intravenous use), and Kesimpta® (ofatumumab injection for subcutaneous use).[2] These agents are not indicated for use in combination. Additional data are required to determine if use of disease-modifying MS agents in combination is safe and provides added efficacy.

23. Non-Relapsing Forms of Multiple Sclerosis.
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis. The efficacy of Avonex has not been established in patients with multiple sclerosis with non-relapsing forms of multiple sclerosis.[1]

24. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

13. Avonex® injection for intramuscular use [prescribing information]. Cambridge, MA: Biogen, Inc.; March 2020.
14. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. September 2019. Available at: http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed on July 31, 2020.
15. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
16. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Zinbryta was removed from the market. Therefore, Zinbryta was deleted from the list of medications in which Avonex should not be used with concomitantly.	08/15/2018
Annual Revision	The following criteria changes were made: **Multiple Sclerosis:** The criteria was changed to require that the patient has a relapsing form of MS. The criteria previously required the patient have a diagnosis of MS or has experienced an attack and is at risk of MS. **Conditions Not Recommended for Approval:** The condition of Non-Relapsing Forms of MS were added as an exclusion. A note is provided that an example of a non-relapsing form is primary progressive MS. Regarding Use with Other Disease-Modifying Agents for MS, the examples were listed as a note with Mavenclad and Mayzent added.	07/17/2019
Annual Revision	The following criteria changes were made: **Conditions Not Recommended for Approval:** Bafiertam, Vumerity, and Zeposia were added to the Note that provides examples of disease-modifying MS agents in which Avonex should not be used with concurrently.	08/05/2020
Selected Revision	**Multiple Sclerosis:** Examples of relapsing forms of MS were added in a Note. **Conditions Not Recommended for Approval:** Regarding Use with Other Disease-Modifying Agents for MS, Kesimpta was added to the list of examples provided in the Note.	09/09/2020

MS – Multiple sclerosis.

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Bafiertam Prior Authorization Policy

- Bafiertam™ (monomethyl fumarate delayed-release capsules – Banner Life Sciences LLC)

REVIEW DATE: 08/05/2020; selected revision 09/09/2020

OVERVIEW

Bafiertam is indicated for the treatment of relapsing forms of multiple sclerosis (MS) to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive MS in adults.[1]

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[2] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[3] as well as in 2017.[4] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-4] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

Safety

Progressive multifocal leukoencephalopathy has occurred in patients with MS treated with Tecfidera® (dimethyl fumarate delayed-release capsules), which is the prodrug of Bafiertam.[1]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Bafiertam. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Bafiertam as well as the monitoring required for adverse events and efficacy, approval requires Bafiertam to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Bafiertam is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Multiple Sclerosis.** Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient has a relapsing form of multiple sclerosis; AND
     Note: Examples of relapsing forms of multiple sclerosis (MS) include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
   - **B)** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Bafiertam is not recommended in the following situations:

153. Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.
Note: Examples of disease modifying agents used for multiple sclerosis include Aubagio® (teriflunomide tablets), Avonex® (interferon beta 1a injection [intramuscular]), Betaseron®/Extavia® (interferon beta-1b injection), Rebif® (interferon beta-1a injection [subcutaneous]), Copaxone®/Glatopa® (glatiramer acetate injection), Plegridy® (peginterferon beta-1a injection), Gilenya® (fingolimod tablets), Mavenclad® (cladribine tablets), Mayzent® (siponomid tablets), Tecfidera® (dimethyl fumarate delayed-release capsules), Vumerity® (diroximel fumarate delayed-release capsules), Ocrevus® (ocrelizumab injection for intravenous use), Tysabri® (natalizumab injection for intravenous infusion), Lemtrada® (alemtuzumab injection for intravenous use), Zeposia® (ozanimod capsules), and Kesimpta® (ofatumumab injection for subcutaneous use).[2] These agents are not indicated for use in combination. Additional data are required to determine if use of disease-modifying MS agents in combination is safe and provides added efficacy.

154. Non-Relapsing Forms of Multiple Sclerosis.
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis. The efficacy of Bafiertam has not been established in patients with multiple sclerosis with non-relapsing forms of multiple sclerosis.[1]

155. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

200. Bafiertam™ delayed-release capsules [prescribing information]. High Point, NC: Banner Life Sciences LLC; April 2020.
201. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. Updated September 2019. Available at: http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed on September 9, 2020.
202. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
203. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	---	05/06/2020
Early Annual Revision	No criteria changes.	08/05/2020
Selected Revision	**Multiple Sclerosis:** Examples of relapsing forms of multiple sclerosis were added in a Note. **Conditions Not Recommended for Approval:** Regarding Use with Other Disease-Modifying Agents for multiple sclerosis, Kesimpta was added to the list of examples provided in the Note.	09/09/2020

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Betaseron/Extavia Prior Authorization Policy

- Betaseron® (interferon beta-1b injection for subcutaneous use – Bayer)
- Extavia® (interferon beta-1b injection for subcutaneous use – Novartis)

REVIEW DATE: 08/05/2020; selected revision 09/09/2020

OVERVIEW

Betaseron and Extavia are indicated for the treatment of relapsing forms of multiple sclerosis (MS) to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults.[1,2] Extavia and Betaseron are essentially the same formulation of interferon beta-1b. The only difference is that Extavia is supplied with a 27 gauge needle compared to a 30 gauge needle that is given with Betaseron.

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[3] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[4] as well as in 2017.[5] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive

MS, and secondary progressive MS.[3-5] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[3] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Betaseron and Extavia. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Betaseron/Extavia as well as the monitoring required for adverse events and long-term efficacy, approval requires Betaseron and Extavia to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Betaseron/Extavia is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Multiple Sclerosis.** Approve for 3 years if the patient meets the following criteria (A and B):
   - **A)** Patient has a relapsing form of multiple sclerosis; AND
     Note: Examples of relapsing forms of multiple sclerosis (MS) include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
   - **B)** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Betaseron/Extavia is not recommended in the following situations:

~~25.~~ **Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.**
Note: Examples of disease modifying agents used for multiple sclerosis include Avonex® (interferon beta 1a injection [intramuscular]), Rebif® (interferon beta-1a injection [subcutaneous]), Copaxone®/Glatopa® (glatiramer acetate injection), Plegridy® (peginterferon beta-1a injection), Aubagio® (teriflunomide tablets), Gilenya® (fingolimod tablets), Mavenclad® (cladribine tablets), Mayzent® (siponimod tablets), Tecfidera® (dimethyl fumarate delayed-release capsules), Bafiertam® (monomethyl fumarate delayed-release capsules), Vumerity® (diroximel fumarate delayed-release capsules), Zeposia® (ozanimod capsules), Ocrevus® (ocrelizumab injection for intravenous use), Tysabri® (natalizumab injection for intravenous infusion), Lemtrada® (alemtuzumab injection for intravenous use), and Kesimpta® (ofatumumab injection for subcutaneous use).[3] These agents are not

indicated for use in combination. Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

26. Non-Relapsing Forms of Multiple Sclerosis.
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis. The efficacy of Betaseron/Extavia have not been established in patients with multiple sclerosis with non-relapsing forms of multiple sclerosis.[1]

27. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

17. Betaseron® injection for subcutaneous use [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals; August 2019.
18. Extavia® injection for subcutaneous use [prescribing information]. East Hanover, NJ: Novartis; August 2019.
19. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. September 2019. Available at: http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed on September 9, 2020.
20. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
21. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Zinbryta was removed from the market. Therefore, Zinbryta was deleted from the list of medications in which Betaseron/Extavia should not be used with concomitantly.	08/15/2018
Annual Revision	The following criteria changes were made: **Multiple Sclerosis:** The criteria was changed to require that the patient has a relapsing form of multiple sclerosis. The criteria previously required the patient have a diagnosis of MS or has experienced an attack and is at risk of MS. **Conditions Not Recommended for Approval:** The condition of Non-Relapsing Forms of MS was added as an exclusion. A note is provided that an example of a non-relapsing form is primary progressive MS. Regarding Use with Other Disease-Modifying Agents for MS, the examples were listed as a note with Mavenclad and Mayzent added.	07/17/2019
Annual Revision	The following criteria changes were made: **Conditions Not Recommended for Approval:** Bafiertam, Vumerity, and Zeposia were added to the Note that provides examples of disease-modifying MS agents in which Betaseron/Extavia should not be used with concurrently.	08/05/2020
Selected Revision	**Multiple Sclerosis:** Examples of relapsing forms of MS were added in a Note. **Conditions Not Recommended for Approval:** Regarding Use with Other Disease-Modifying Agents for MS, Kesimpta was added to the list of examples provided in the Note.	09/09/2020

MS – Multiple sclerosis.

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Dimethyl Fumarate (Tecfidera) Prior Authorization Policy

- Tecfidera® (dimethyl fumarate delayed-release capsules – Biogen, generic)

REVIEW DATE: 08/05/2020; selected revision 09/09/2020

OVERVIEW

Dimethyl fumarate is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive MS in adults.[1]

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[2] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[3] as well as in 2017.[4] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-4] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

Safety

Progressive multifocal leukoencephalopathy has occurred in patients with MS treated with dimethyl fumarate, including a fatal case.[1]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of dimethyl fumarate. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with dimethyl fumarate as well as the monitoring required for adverse events and efficacy, approval requires dimethyl fumarate to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of dimethyl fumarate is recommended in those who meet the following criteria:

FDA-Approved Indication

1. Multiple Sclerosis. Approve for 1 year if the patient meets the following criteria (A and B):
- **C)** Patient has a relapsing form of multiple sclerosis; AND
  Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
- **D)** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of dimethyl fumarate is not recommended in the following situations:

156. Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis. Note: Examples of disease modifying agents used for multiple sclerosis include Aubagio® (teriflunomide tablets), Avonex® (interferon beta 1a injection [intramuscular]), Betaseron®/Extavia® (interferon beta-1b injection), Rebif® (interferon beta-1a injection [subcutaneous]), Copaxone®/Glatopa® (glatiramer acetate injection), Plegridy® (peginterferon beta-1a injection), Gilenya® (fingolimod tablets), Mavenclad® (cladribine tablets), Mayzent® (siponomid tablets), Bafiertam® (monomethyl fumarate delayed-release capsules), Vumerity® (diroximel fumarate delayed-release capsules), Zeposia® (ozanimod capsules), Ocrevus® (ocrelizumab injection for intravenous use), Tysabri® (natalizumab injection for intravenous infusion), Lemtrada® (alemtuzumab injection for intravenous use), and Kesimpta® (ofatumumab injection for subcutaneous use).[2] These agents are not indicated for use in combination. Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

157. Non-Relapsing Forms of Multiple Sclerosis.
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis. The efficacy of dimethyl fumarate has not been established in patients with multiple sclerosis with non-relapsing forms of multiple sclerosis.[1]

158. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

204. Tecfidera® delayed-release capsules [prescribing information]. Cambridge, MA: Biogen; February 2020.
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206. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
207. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Zinbryta was removed from the market. Therefore, Zinbryta was deleted from the list of medications in which Tecfidera should not be used with concomitantly.	08/15/2018
Annual Revision	The wording of "for PSM" was removed from the document title. The following criteria changes were made. **Multiple Sclerosis:** The examples of relapsing forms of MS were removed. **Conditions Not Recommended for Approval:** For patients with Non-Relapsing forms of MS, the example of primary progressive MS is now listed as a note. Regarding Use with Other Disease-Modifying Agents for MS, the examples are now listed as a note with Mavenclad and Mayzent added.	07/17/2019
Annual Revision	The following criteria changes were made: **Conditions Not Recommended for Approval:** Bafiertam, Vumerity, and Zeposia were added to the Note that provides examples of disease-modifying MS agents in which Aubagio should not be used with concurrently.	08/05/2020
Selected Revision	The name of the Policy was changed to reflect its generic availability (Dimethyl Fumarate [Tecfidera]). It was noted that a generic to Tecfidera is available. **Multiple Sclerosis:** Examples of relapsing forms of MS were added in a Note. **Conditions Not Recommended for Approval:** Regarding Use with Other Disease-Modifying Agents for MS, Kesimpta was added to the list of examples provided in the Note.	09/09/2020

PSM – Preferred Specialty Management; MS – Multiple sclerosis.

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Gilenya Prior Authorization Policy

- Gilenya® (fingolimod capsules – Novartis)

REVIEW DATE: 08/05/2020; selected revision 09/09/2020

OVERVIEW

Gilenya, a sphingosine 1-phosphate receptor modulator, is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease in patients 10 years of age and older.[1]

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[2] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS).

Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[3] as well as in 2017.[4] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-4] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.[2] The American Academy of Neurology has practice guidelines regarding disease-modifying therapies for adults with MS.[5] The guidelines cites Gilenya as one of the agents to consider for patients with MS who have highly active disease.

Safety

The initiation of Gilenya leads to decreases in heart rate.[1] After the first dose of Gilenya, the heart rate decreases are noted within an hour and generally are greatest at 6 hours, although the effects can be observed 24 hours after the first dose in some patients. The first dose of Gilenya should be given in a setting with resources to appropriately manage symptomatic bradycardia. Observe patients for 6 hours after the first Gilenya dose for signs and symptoms of bradycardia. Patients with prolonged QTc interval at baseline or during the observation period, or taking medications with known risks of torsades de pointes, should be observed overnight with continuous electrocardiographic (ECG) monitoring. When restarting Gilenya after discontinuation for more than 14 days after the first treatment month, perform first-dose monitoring. There are several contraindications for use which mainly include patients with background cardiovascular disease. Gilenya is associated with serious toxicities such as decreased heart rate and/or atrioventricular condition after the first dose; an increased risk of infections; macular edema; pulmonary toxicity; and elevated liver enzymes. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients who were given Gilenya in the postmarketing setting.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Gilenya. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Gilenya as well as the monitoring required for adverse events and efficacy, approval requires Gilenya to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Gilenya is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Multiple Sclerosis.** Approve for 1 year if the patient meets all of the following criteria (A and B):
   - **A)** Patient has a relapsing form of multiple sclerosis; AND
     Note: Examples of relapsing forms of multiple sclerosis (MS) include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
   - **B)** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Gilenya is not recommended in the following situations:

159. Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.
Note: Examples of disease-modifying agents used for multiple sclerosis include Avonex® (interferon beta 1a injection [intramuscular]), Betaseron®/Extavia® (interferon beta-1b injection), Rebif® (interferon beta-1a injection [subcutaneous]), Copaxone®/Glatopa® (glatiramer acetate injection), Plegridy® (peginterferon beta-1a injection), Aubagio® (teriflunomide tablets), Mavenclad® (cladribine tablets), Mayzent® (siponimod tablets), Tecfidera® (dimethyl fumarate delayed-release capsules), Bafiertam® (monomethyl fumarate delayed-release capsules), Vumerity® (diroximel fumarate delayed-release capsules), Zeposia® (ozanimod capsules), Ocrevus® (ocrelizumab injection for intravenous use), Tysabri® (natalizumab injection for intravenous infusion), Lemtrada® (alemtuzumab injection for intravenous use), and Kesimpta® (ofatumumab injection for subcutaneous use).[2] These agents are not indicated for use in combination. Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

160. Non-Relapsing Forms of Multiple Sclerosis.
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis. In the INFORMS trial Gilenya did not slow disease progression in patients with primary progressive multiple sclerosis.[6]

161. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

208. Gilenya® capsules [prescribing information]. East Hanover, NJ: Novartis; December 2019.
209. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. September 2019. Available at: http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed on September 9, 2020.
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HISTORY

Type of Revision	Summary of Changes	Review Date

Annual Revision	Zinbryta was removed from the market. Therefore, Zinbryta was deleted from the list of medications in which Gilenya should not be used with concomitantly.	08/15/2018
Annual Revision	The wording of "for PSM" was removed from the document title. The following criteria changes were made. **Multiple Sclerosis:** The examples of relapsing forms of MS were removed. **Conditions Not Recommended for Approval:** For patients with Non-Relapsing Forms of MS, the example of primary progressive MS is now listed as a note. Regarding Use with Other Disease-Modifying Agents for MS, the examples are now listed as a note with Mavenclad and Mayzent added.	07/17/2019
Annual Revision	The following criteria changes were made: **Conditions Not Recommended for Approval:** Bafiertam, Vumerity, and Zeposia were added to the Note that provides examples of disease-modifying MS agents in which Gilenya should not be used with concurrently.	08/05/2020
Selected Revision	**Multiple Sclerosis:** Examples of relapsing forms of MS were added in a Note. **Conditions Not Recommended for Approval:** Regarding Use with Other Disease-Modifying Agents for MS, Kesimpta was added to the list of examples provided in the Note.	09/09/2020

PSM – Preferred Specialty Management; MS – Multiple sclerosis.

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Glatiramer Products Prior Authorization Policy

- Copaxone® (glatiramer acetate for subcutaneous injection [20 mg/mL and 40 mg/mL] – Teva, generic)
- Glatopa® (glatiramer acetate for subcutaneous injection [20 mg/mL and 40 mg/mL] – Sandoz)

REVIEW DATE: 08/05/2020; selected revision 09/09/2020

OVERVIEW

Copaxone, Glatopa and generic glatiramer acetate are indicated for the treatment of relapsing forms of multiple sclerosis (MS) to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease, in adults.[1-4]

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[5] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[6] as well as in 2017.[7] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[5-7] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease

(or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[5] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Copaxone (20 mg/mL and 40 mg/mL) and Glatopa (20 mg/mL and 40 mg/mL). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Copaxone/Glatopa as well as the monitoring required for adverse events and long-term efficacy, approval requires Copaxone/Glatopa to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of glatiramer is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Multiple Sclerosis.** Approve for 3 years if the patient meets the following criteria (A and B):
   - **T)** Patient has a relapsing form of multiple sclerosis; AND
     Note: Examples of relapsing forms of multiple sclerosis (MS) include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
   - **U)** Medication is prescribed by or in consultation with, a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of glatiramer is not recommended in the following situations:

28. **Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.**
    Note: Examples of disease modifying agents used for multiple sclerosis include Avonex® (interferon beta-1a injection [intramuscular]), Betaseron®/Extavia® (interferon beta-1b injection), Rebif® (interferon beta-1a injection [subcutaneous]), Plegridy® (peginterferon beta-1a injection), Aubagio® (teriflunomide tablets), Gilenya® (fingolimod tablets), Mavenclad® (cladribine tablets), Mayzent® (siponimod tablets), Tecfidera® (dimethyl fumarate delayed-release capsules), Bafiertam® (monomethyl fumarate delayed-release capsules), Vumerity® (diroximel fumarate delayed-release capsules), Zeposia® (ozanimod capsules), Ocrevus® (ocrelizumab injection for intravenous use), Tysabri® (natalizumab injection for intravenous infusion), Lemtrada® (alemtuzumab injection for intravenous use), and Kesimpta® (ofatumumab injection for subcutaneous use).[2] These agents are not indicated for use in combination. Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

29. **Non-Relapsing Forms of Multiple Sclerosis.**

Note: An example of non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis. The efficacy of Copaxone and Glatopa have not been established in patients with multiple sclerosis with non-relapsing forms of multiple sclerosis.[1-4]

30. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

22. Copaxone® injection for subcutaneous use [prescribing information]. Overland Park, KS and North Wales, PA: Teva Neuroscience and Teva Pharmaceuticals; July 2020.
23. Glatopa® injection for subcutaneous use [prescribing information]. Princeton, NJ: Sandoz; January 2020.
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28. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.

HISTORY

Type of Revision	Summary of Changes	Review Date
Selected Revision	Glatopa 40 mg/mL was added to the policy.	2/21/2018
Annual Revision	Zinbryta was removed from the market. Therefore, Zinbryta was deleted from the list of medications in which Copaxone/Glatopa should not be used with concomitantly.	08/15/2018
Annual Revision	The Policy name was changed to Glatiramer Products (previously stated Copaxone/Glatopa). The following criteria changes were made: **Multiple Sclerosis:** The criteria was changed to require that the patient has a relapsing form of multiple sclerosis. The criteria previously required the patient have a diagnosis of MS or has experienced an attack and is at risk of MS. **Conditions Not Recommended for Approval:** The condition of Non-Relapsing Forms of MS was added as an exclusion. A note is provided that an example of a non-relapsing form is primary progressive MS. Regarding Use with Other Disease-Modifying Agents for MS, the examples are now listed as a note with Mavenclad and Mayzent added.	07/17/2019
Annual Revision	The following criteria changes were made: **Conditions Not Recommended for Approval:** Bafiertam, Vumerity, and Zeposia were added to the Note that provides examples of disease-modifying MS agents in which glatiramer products should not be used with concurrently.	08/05/2020
Selected Revision	**Multiple Sclerosis:** Examples of relapsing forms of MS were added in a Note. **Conditions Not Recommended for Approval:** Regarding Use with Other Disease-Modifying Agents for MS, Kesimpta was added to the list of examples provided in the Note.	09/09/2020

MS – Multiple sclerosis.

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Kesimpta Prior Authorization Policy

- Kesimpta® (ofatumumab injection for subcutaneous use – Novartis)

REVIEW DATE: 08/26/2020

OVERVIEW

Kesimpta, a CD20-directed cytolytic antibody, is indicated for the treatment of relapsing forms of multiple sclerosis (MS) to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive MS in adults.[1]

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[2] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns.

Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[3] as well as in 2017.[4] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-4] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Kesimpta. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Kesimpta as well as the monitoring required for adverse events and long-term efficacy, approval requires Kesimpta to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kesimpta is recommended in those who meet the following criteria:

FDA-Approved Indications

130. Multiple Sclerosis. Approve for 1 year if the patient meets the following criteria (A, B and C):
- **A)** Patient has a relapsing form of multiple sclerosis; AND
- **B)** Patient is ≥ 18 years; AND
- **C)** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kesimpta is not recommended in the following situations:

162. Concurrent Use with Other Disease Modifying Agents Used for Multiple Sclerosis.

Note: Examples of disease modifying agents used for multiple sclerosis include Aubagio® (teriflunomide tablets), Avonex® (interferon beta 1a injection for intramuscular use), Betaseron®/Extavia® (interferon beta-1b injection for subcutaneous use), Rebif® (interferon beta-1a injection for subcutaneous use), Copaxone®/Glatopa® (glatiramer acetate injection for subcutaneous use), glatiramer acetate injection, Plegridy® (peginterferon beta-1a injection for subcutaneous use), Tecfidera® (dimethyl fumarate delayed-release capsules), Gilenya® (fingolimod capsules), Mavenclad® (cladribine tablets), Mayzent® (siponomid tablets), Bafiertam® (monomethyl fumarate delayed-release capsules), Vumerity® (diroximel fumarate delayed-release capsules), Zeposia® (ozanimod capsules), Ocrevus® (ocrelizumab injection for intravenous use), Tysabri® (natalizumab injection for intravenous infusion), and Lemtrada® (alemtuzumab injection for intravenous use).[2] These agents are not indicated for use in

combination. Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe provides added efficacy.

163. Non-Relapsing Forms of Multiple Sclerosis.
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis. The efficacy of Kesimpta has not been established in patients with multiple sclerosis with non-relapsing forms of multiple sclerosis.[1]

164. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/26/2020

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Lemtrada Prior Authorization Policy

- Lemtrada® (alemtuzumab injection for intravenous use – Genzyme)

REVIEW DATE: 11/11/2020

OVERVIEW

Lemtrada, a CD52-directed cytolytic monoclonal antibody, is indicated for the treatment of patients with relapsing forms of **multiple sclerosis** (MS) to include relapsing remitting disease and active secondary progressive MS in adults.[1] Lemtrada is not recommended for use in patients with clinically isolated syndrome because of its safety profile.

Due to its safety profile, use of Lemtrada should generally be reserved for patients who have had an inadequate response to two or more medications indicated for the treatment of MS.[1] Lemtrada contains the same active ingredient found in Campath® (alemtuzumab injection for intravenous use). The safety and efficacy of Lemtrada have not been established in pediatric patients < 17 years of age.

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system that impacts almost 1,000,000 people in the US.[2] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a

relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[3] as well as in 2017.[4] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-4] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

A practice guideline recommendation regarding disease-modifying agents for adults with MS from the American Academy of Neurology (2018) states to consider Lemtrada for patients with MS who have highly active disease.[5]

Safety

Lemtrada is available only through a restricted Risk Evaluation Mitigation Strategy (REMS) program called the LEMTRADA REMS Program due to the risks of autoimmunity, infusion reactions, stroke, and malignancies.[1] Use of Lemtrada is contraindicated in patients who has infection with human immunodeficiency virus and those with active infection. Progressive multifocal leukoencephalopathy has occurred in a patient with MS who received Lemtrada.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lemtrada. All approvals are noted for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lemtrada, as well as the monitoring required for adverse events and long-term efficacy, approval requires Lemtrada to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Lemtrada at initiation as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes magnetic resonance imaging (MRI) reports, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lemtrada injection is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Multiple Sclerosis.** Approve for the duration noted if the patient meets one of the following (A or B):

A) Initial Therapy (this includes patients who have started but not completed the first course of Lemtrada Therapy). Approve for 5 days in patients who meet all of the following criteria (i, ii, iii, and iv):

i. Patient is ≥ 17 years of age; AND

ii. Patient has a relapsing form of multiple sclerosis; AND
Note: Examples of relapsing forms of multiple sclerosis include relapsing remitting disease and active secondary progressive disease.

iii. Patient meets one of the following (a or b):

a) According to the prescriber the patient has experienced inadequate efficacy or significant intolerance to two disease-modifying agents used for multiple sclerosis; OR
Note: Examples include Avonex® (interferon beta-1a injection [intramuscular]), Rebif® (interferon beta-1a injection [subcutaneous]), Betaseron®/Extavia® (interferon beta-1b injection), glatiramer acetate injection (Copaxone®/Glatopa®, generic), Plegridy® (peginterferon beta-1a injection), Gilenya® (fingolimod capsules), Aubagio® (teriflunomide tablets), Mavenclad® (cladribine tablets), Mayzent® (siponimod tablets), Vumerity® (diroximel fumarate delayed-release capsules), Tysabri® (natalizumab injection for intravenous use), Bafiertam™ (monomethyl fumarate delayed-release capsules), dimethyl fumarate delayed-release capsules (Tecfidera®, generic), Zeposia® (ozanimod capsules), Kesimpta® (ofatumumab injection for subcutaneous use), and Ocrevus® (ocrelizumab injection for intravenous use).

b) According to the prescriber, the patient has highly active or aggressive multiple sclerosis by meeting one of the following [(1), (2), (3), or (4)]:

(1) Patient has demonstrated rapidly-advancing deterioration(s) in physical functioning (e.g., loss of mobility/or lower levels of ambulation, severe changes in strength or coordination) **[documentation required]**; OR

(2) Disabling relapse(s) with suboptimal response to systemic corticosteroids **[documentation required]**; OR

(3) Magnetic resonance imaging [MRI] findings suggest highly-active or aggressive multiple sclerosis (e.g., new, enlarging, or a high burden of T2 lesions or gadolinium-enhancing lesions) **[documentation required]**; OR

(4) Manifestations of multiple sclerosis-related cognitive impairment **[documentation required]**; AND

iv. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR

B) Patient Who Has Completed a Previous Lemtrada Therapy Course. Approve for 3 days if the patient meets all of the following (i, ii, iii and iv):

i. Patient is ≥ 17 years of age; AND

ii. Patient has a relapsing form of multiple sclerosis; AND
Note: Examples of relapsing forms of multiple sclerosis include relapsing remitting disease and active secondary progressive disease.

iii. At least 12 months has elapsed from the last dose of any prior Lemtrada treatment course; AND

iv. Medication is prescribed by or in consultation with a neurologist or a physician that specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lemtrada is not recommended in the following situations:

1. **Clinically Isolated Syndrome.** Lemtrada is not recommended for use in patients with clinically isolated syndrome due to its safety profile.[1]

2. **Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.** Lemtrada should not be given in combination with other disease-modifying agents used for multiple sclerosis. Concomitant use of Lemtrada with immunosuppreisve therapies could increase the risk of immunosuppression.
   Note: Examples include Avonex® (interferon beta-1a injection [intramuscular]), Rebif® (interferon beta-1a injection [subcutaneous]), Betaseron®/Extavia® (interferon beta-1b injection), glatiramer acetate injection (Copaxone®/Glatopa®, generic), Plegridy® (peginterferon beta-1a injection), Gilenya® (fingolimod capsules), Aubagio® (teriflunomide tablets), Mavenclad® (cladribine tablets), Mayzent® (siponimod tablets), Vumerity® (diroximel fumarate delayed-release capsules), Tysabri® (natalizumab injection for intravenous use), Bafiertam™ (monomethyl fumarate delayed-release capsules), dimethyl fumarate delayed-release capsules (Tecfidera®, generic), Zeposia® (ozanimod capsules), Kesimpta® (ofatumumab injection for subcutaneous use), and Ocrevus® (ocrelizumab injection for intravenous use).

3. **Human Immunodeficiency Virus (HIV) Infection.** Use of Lemtrada is contraindicated in patients who are infected with HIV because Lemtrada causes prolonged reductions of CD4+ lymphocyte counts.[1]

4. **Non-Relapsing Forms of Multiple Sclerosis.** The efficacy of Lemtrada has not been established in patients with multiple sclerosis with non-relapsing forms of the disease.[1]
   Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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201. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018;90:777-788.

HISTORY

Type of Revision	Summary of Changes	Review Date
Selected Revision	**1. Multiple Sclerosis:** The phrase "Relapsing forms" (of MS) was removed from the cited indication. For initial therapy, Mavenclad and Mayzent were added among the list of disease-modifying MS agents that count as a trial towards the requirement that patients must have tried two agents and had an inadequate response or are unable to tolerate. The criteria were revised to reflect the recent change to the prescribing information that more than two Lemtrada treatment courses can be given. The wording which described directives following completion of "one prior course of Lemtrada" was changed to state that the patient "has completed a previous course" with the requirement added that at least 12 months has elapsed from the last dose of any prior Lemtrada treatment course. **2. Conditions Not Recommended for Approval:** The condition of Patient with Relapsing Forms of MS who is Requesting a Third (or more) Course of Lemtrada Therapy	05/29/2019

	was removed. For clarity, Mavenclad and Mayzent were added to the list of disease-modifying MS therapies in which Lemtrada should not be used with concomitantly.	
Annual Revision	The following criteria changes were made: 1. **Multiple Sclerosis:** The phrase "Relapsing forms" was removed from the stated indication. Criteria were revised such that the examples of relapsing forms of MS were removed. The word "prescriber" replaced the phrase of "prescribing physician" in applicable criteria. Vumerity and glatiramer acetate injection were added as medications trials that count toward the requirement of a trial of two disease-modifying agents used for MS. 2. **Conditions Not Recommended for Approval:** "Children with MS Who Are < 17 Years of Age" was removed as this is duplicative to the requirement in the approval criteria. The Regarding "Concurrent Use with Other Disease-Modifying Agents for MS", the examples of glatiramer acetate injection, Vumerity, Mavenclad and Mayzent were added. The criteria that stated "Primary Progressive (Chronic Progressive) MS was changed to state "Non-Relapsing Forms of MS" with a note that an example is Primary Progressive MS. Clinically Isolated Syndrome was added as a Condition Not Recommended for Approval as now recommended in the Lemtrada prescribing information.	11/13/2019
Annual Revision	The following changes were made: 1. **Multiple Sclerosis:** For the criteria that requires that the patient try two other disease-modifying medications for MS, the wording regarding this trial was changed from and "has had an inadequate response or is unable to tolerate" to "has experienced inadequate efficacy or significant intolerance." Also, examples of MS disease-modifying therapies were added to the Note. A Note was added after the requirement that the patient have a relapsing form of MS that examples of relapsing forms of MS include relapsing remitting disease and active secondary progressive disease. 2. **Conditions Not Recommended for Approval:** For the criteria regarding "Concurrent Use with Other Disease-Modifying Agents Used for MS", additional agents were added. For the condition of HIV, the phrase "Patients With" was removed from the cited condition.	11/11/2020

MS – Multiple sclerosis; HIV – Human immunodeficiency virus.

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Mavenclad Prior Authorization Policy

- Mavenclad® (cladribine tablets – EMD Serono)

REVIEW DATE: 08/05/2020; selected revision 09/09/2020

OVERVIEW

Mavenclad, a purine antimetabolite, is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing remitting disease, and active secondary progressive disease, in adults.[1] Due to its safety profile, use of Mavenclad is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternative drug for the treatment of MS.[1] A limitation of use is that Mavenclad is not recommended for use in patients with clinically isolated syndrome because of its safety profile.

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[2] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS).

Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[3] as well as in 2017.[4] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-4] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

Safety

Mavenclad has a Boxed Warning regarding malignancies and the risk of teratogenicity.[1] Mavenclad may increase the risk of malignancy. Also, Mavenclad is a cytotoxic drug. Special handling instructions and disposal procedures should be followed. There are several contraindications associated with the use of Mavenclad including: patients with current malignancy; pregnant women, women and men of reproductive potential who do not plan to use effective contraception during Mavenclad dosing and for 6 months after the last dose in each treatment course; human immunodeficiency virus (HIV); active chronic infection (e.g., hepatitis or tuberculosis); history of hypersensitivity to cladribine; and women intending to breastfeed on a treatment day in which Mavenclad is administered and for 10 days after the last dose. Warnings and Precautions for Mavenclad include lymphopenia, infections, hematologic toxicity, graft-versus-host disease with blood transfusion, and liver injury.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Mavenclad. All approvals are provided for the duration cited below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Mavenclad as well as the monitoring required for adverse events and long-term efficacy, approval requires Mavenclad to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mavenclad is recommended in those who meet the following criteria:

FDA-Approved Indications

3. **Multiple Sclerosis.** Approve for 1 year if the patient meets the following criteria (A and B):
   - **C)** Patient has a relapsing form of multiple sclerosis; AND
     Note: Examples of relapsing forms of multiple sclerosis include relapsing-remitting disease and active secondary progressive disease.

D) Medication is prescribed by or in consultation with a neurologist or a physician that specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Mavenclad is not recommended in the following situations:

165. Clinically Isolated Syndrome. Mavenclad is not recommended for use in patients with clinically isolated syndrome due to its safety profile.[1]

166. Current Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.
Note: Examples of disease modifying agents used for multiple sclerosis include Avonex® (interferon beta 1a injection [intramuscular]), Betaseron®/Extavia® (interferon beta-1b injection), Rebif® (interferon beta-1a injection [subcutaneous]), Copaxone®/Glatopa® (glatiramer acetate injection), Plegridy® (peginterferon beta-1a injection), Aubagio® (teriflunomide tablets), Gilenya® (fingolimod tablets), Mayzent® (siponimod tablets), Tecfidera® (dimethyl fumarate delayed-release capsules), Bafiertam® (monomethyl fumarate delayed-release capsules), Vumerity® (diroximel fumarate delayed-release capsules), Zeposia® (ozanimod capsules), Ocrevus® (ocrelizumab injection for intravenous use), Tysabri® (natalizumab injection for intravenous infusion), Lemtrada® (alemtuzumab injection for intravenous use), and Kesimpta® (ofatumumab injection for subcutaneous use).[2] These agents are not indicated for use in combination. Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

167. Non-Relapsing Forms of Multiple Sclerosis.
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis. The efficacy of Mavenclad has not been established in patients with multiple sclerosis with non-relapsing forms of the disease.[1]

168. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	04/01/2019
Selected Revision	The criterion that required a patient to have tried at least one other disease-modifying agent for multiple sclerosis and to have had an inadequate response to this therapy according to the prescribing physician was removed.	06/12/2019
Early Annual Revision	The following criteria changes were made. **Multiple Sclerosis:** The criterion that required that the patient has a relapsing form of MS was revised to remove the phrase that state "to include relapsing remitting MS or active secondary progressive MS forms".	07/17/2019

	Conditions Not Recommended for Approval: For Patients with Non-Relapsing Forms of MS, the example of primary progressive MS is now listed as a note. Regarding Use with Other Disease-Modifying Agents for MS, the examples are now listed as a note.	
Annual Revision	The following criteria changes were made: **Conditions Not Recommended for Approval:** Bafiertam, Vumerity, and Zeposia were added to the Note that provides examples of disease-modifying MS agents in which Mavenclad should not be used with concurrently.	08/05/2020
Selected Revision	**Multiple Sclerosis:** Examples of relapsing forms of MS were added in a Note. **Conditions Not Recommended for Approval:** Regarding Use with Other Disease-Modifying Agents for MS, Kesimpta was added to the list of examples provided in the Note.	09/09/2020

MS – Multiple sclerosis.

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Mayzent Prior Authorization Policy

- Mayzent® (siponimod tablets – Novartis)

REVIEW DATE: 08/05/2020; selected revision 09/09/2020

OVERVIEW

Mayzent, a sphingosine 1-phosphate receptor modulator, is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease in adults.[1]

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[2] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[3] as well as in 2017.[4] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-4] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

Safety

The initiation of Mayzent leads to decreases in heart rate.[1] First-dose 6-hour monitoring is recommended in certain patients with preexisting cardiac conditions. Additional monitoring beyond 6 hours may also be required. After the initial titration is complete, if Mayzent therapy is interrupted for four or more consecutive daily doses, reinitiate treatment with Day 1 of the titration regimen and also complete first-dose monitoring for patients for whom it is recommended. The most common adverse events with Mayzent include headache, hypertension, and transaminase elevations. Mayzent has Warnings/Precautions regarding infections, macular edema, bradyarrhythmias and atrioventricular conduction delays, respiratory effects, liver injury, increased blood pressure, and posterior reversible encephalopathy syndrome.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Mayzent. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Mayzent as well as the monitoring required for adverse events and long-term efficacy, approval requires Mayzent to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mayzent is recommended in those who meet the following criteria:

FDA-Approved Indications

4. Multiple Sclerosis. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient has a relapsing form of multiple sclerosis; AND
Note: Examples of relapsing forms of multiple sclerosis (MS) include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

B) Medication is prescribed by or in consultation with neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Mayzent is recommended in those who meet the following criteria:

169. Current Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.

Note: Examples of disease-modifying agents used for multiple sclerosis include Avonex® (interferon beta 1a injection [intramuscular]), Betaseron®/Extavia® (interferon beta-1b injection), Rebif® (interferon beta-1a injection [subcutaneous]), Copaxone®/Glatopa® (glatiramer acetate injection), Plegridy® (peginterferon beta-1a injection), Aubagio® (teriflunomide tablets), Gilenya® (fingolimod tablets), Mavenclad® (cladribine tablets), Tecfidera® (dimethyl fumarate delayed-release capsules), Bafiertam® (monomethyl fumarate delayed-release capsules), Vumerity® (diroximel fumarate delayed-release capsules), Zeposia® (ozanimod capsules), Ocrevus® (ocrelizumab injection for intravenous use), Tysabri® (natalizumab injection for intravenous infusion), Lemtrada® (alemtuzumab injection for intravenous use), and Kesimpta® (ofatumumab injection for subcutaneous use).[2] These agents are not

indicated for use in combination. Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

170. Non-Relapsing Forms of Multiple Sclerosis.
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis. The efficacy of Mayzent has not been established in patients with multiple sclerosis with non-relapsing forms of the disease.[1]

171. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

206. Mayzent® tablets [prescribing information]. East Hanover, NJ: Novartis; March 2019.
207. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. September 2019. Available at: http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed on September 9, 2020.
208. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
209. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	03/27/2019
Early Annual Revision	The following criteria changes were made. **Multiple Sclerosis:** The criterion that requires that the patient has a relapsing form of MS was revised to remove the phrase that stated "to include relapsing remitting MS or active secondary progressive MS". **Conditions Not Recommended for Approval:** For patients with Non-Relapsing Forms of MS, the example of primary progressive MS is now listed as a note. Regarding Use with Other Disease-Modifying Agents for MS, the examples were listed as a note with Mavenclad added.	07/17/2019
Annual Revision	The following criteria changes were made: **Conditions Not Recommended for Approval:** Bafiertam, Vumerity, and Zeposia were added to the Note that provides examples of disease-modifying MS agents in which Mayzent should not be used with concurrently.	08/05/2020
Selected Revision	**Multiple Sclerosis:** Examples of relapsing forms of MS were added in a Note. **Conditions Not Recommended for Approval:** Regarding Use with Other Disease-Modifying Agents for MS, Kesimpta was added to the list of examples provided in the Note.	09/09/2020

MS – Multiple sclerosis.

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Ocrevus Prior Authorization Policy

- Ocrevus® (ocrelizumab injection for intravenous use – Genentech/Roche)

REVIEW DATE: 11/11/2020

OVERVIEW

Ocrevus is a CD20-directed cytolytic antibody indicated for the treatment of adults with:[1]

- **Relapsing forms of multiple sclerosis** (MS) to include to include clinically isolated syndrome, relapsing remitting MS, and active secondary progressive MS.

- **Primary progressive MS**.

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system that impacts almost 1,000,000 people in the US.[2] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[3] as well as in 2017.[4] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-4] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ocrevus. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ocrevus as well as the monitoring required for adverse events and long-term efficacy, approval requires Ocrevus to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: None.
Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ocrevus is recommended in those who meet the following criteria:

FDA-Approved Indications

2. **Multiple Sclerosis, Relapsing Forms.** Approve for 1 year if the patient meets all of the following criteria (A, B, and C):
   - **E)** Patient is ≥ 18 years of age; AND
   - **F)** Patient has a relapsing form of multiple sclerosis; AND
     Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

G) Medication is prescribed by or in consultation with a physician who specializes in the treatment of MS and/or a neurologist.

29. Multiple Sclerosis, Primary Progressive. Approve for 1 year if the patient meets all of the following criteria (A and B):

79. Patient is ≥ 18 years of age; AND

80. Medication is prescribed by or in consultation with a physician who specializes in the treatment of MS and/or a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ocrevus is not recommended in the following situations:

172. Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis. Ocrevus is not indicated for use in combination with other multiple sclerosis disease-modifying therapies and the safety and efficacy have not been adequately established. The concomitant use of Ocrevus with other immune-modulating or immunosuppressive therapies is anticipated to increase the risk of immunosuppression.[1]

Note: Examples include Avonex® (interferon beta-1a injection [intramuscular]), Rebif® (interferon beta-1a injection [subcutaneous]), Betaseron®/Extavia® (interferon beta-1b injection), glatiramer acetate injection (Copaxone®/Glatopa®, generic), Plegridy® (peginterferon beta-1a injection), Gilenya® (fingolimod capsules), Aubagio® (teriflunomide tablets), Mavenclad® (cladribine tablets), Mayzent® (siponimod tablets), Vumerity® (diroximel fumarate delayed-release capsules), Tysabri® (natalizumab injection for intravenous use), Bafiertam™ (monomethyl fumarate delayed-release capsules), dimethyl fumarate delayed-release capsules (Tecfidera®, generic), Zeposia® (ozanimod capsules), Kesimpta® (ofatumumab injection for subcutaneous use), and Lemtrada® (alemtuzumab injection for intravenous use).

173. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

208. Ocrevus® injection for intravenous infusion [prescribing information]. San Francisco, CA: Genentech, Inc (a Member of the Roche Group); May 2020.
209. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. Updated September 2019. Available at: https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/DMT_Consensus_MS_Coalition.pdf. Accessed on November 6, 2020.
210. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
211. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Removed Zinbryta from the list of medications in which Ocrevus should not be used with concomitantly.	03/21/2018
Early Annual Revision	Changed the approval durations from 3 years to 1 year for both relapsing forms of multiple sclerosis and primary progressive multiple sclerosis.	10/31/2018
Annual Revision	The following criteria changes were made: **3. Multiple Sclerosis, Relapsing Forms:** Criteria were revised such that the examples of relapsing forms of multiple sclerosis were removed.	11/13/2019

	4. Conditions Not Recommended for Approval: Regarding Concurrent Use with Other Disease-Modifying Agents for Multiple Sclerosis", the examples of glatiramer acetate injection, Vumerity, Mavenclad and Mayzent added.	
Annual Revision	The following changes were made: **3. Multiple Sclerosis:** A Note was added after the requirement that the patient have a relapsing form of multiple sclerosis that examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease and active secondary progressive disease. **4. Conditions Not Recommended for Approval:** For the criteria regarding "Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis", examples of agents were added in the Note.	11/11/2020

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Plegridy Prior Authorization Policy

- Plegridy® (peginterferon beta-1a injection for subcutaneous or intramuscular use – Biogen Idec)

REVIEW DATE: 08/05/2020; selected revision 09/09/2020 and 02/17/2021

OVERVIEW

Plegridy, an interferon beta product, is indicated for the treatment of relapsing forms of multiple sclerosis (MS) to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease in adults.[1]

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system that impacts almost 1,000,000 people in the US.[2] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[3] as well as in 2017.[4] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-4] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Plegridy. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Plegridy as well as the monitoring required for adverse events and long-term efficacy, approval requires Plegridy to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Plegridy is recommended in those who meet the following criteria:

FDA-Approved Indication

2. Multiple Sclerosis. Approve for 3 years if the patient meets the following criteria (A and B):

V) Patient has a relapsing form of multiple sclerosis; AND
Note: Examples of relapsing forms of multiple sclerosis (MS) include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

W) Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Plegridy is not recommended in the following situations:

31. Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.
Note: Examples of disease modifying agents used for multiple sclerosis include Avonex® (interferon beta-1a injection [intramuscular]), Betaseron®/Extavia® (interferon beta-1b injection), Rebif® (interferon beta-1a injection [subcutaneous]), Copaxone®/Glatopa® (glatiramer acetate injection), Aubagio® (teriflunomide tablets), Gilenya® (fingolimod tablets), Mavenclad® (cladribine tablets), Mayzent® (siponimod tablets), Tecfidera® (dimethyl fumarate delayed-release capsules), Bafiertam® (monomethyl fumarate delayed-release capsules), Vumerity® (diroximel fumarate delayed-release capsules), Zeposia® (ozanimod capsules), Ocrevus® (ocrelizumab injection for intravenous use), Tysabri® (natalizumab injection for intravenous infusion), Lemtrada® (alemtuzumab injection for intravenous use), and Kesimpta® (ofatumumab injection for subcutaneous use).[2] These agents are not indicated for use in combination. Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

32. Non-Relapsing Forms of Multiple Sclerosis.
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis. The efficacy of Plegridy has not been established in patients with multiple sclerosis with non-relapsing forms of multiple sclerosis.[1]

33. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

29. Plegridy® injection for subcutaneous or intramuscular use [prescribing information]. Cambridge, MA: Biogen, Idec; January 2021.
30. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. September 2019. Available at: http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed on September 9, 2020.
31. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
32. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	The following criteria changes were made: **Multiple Sclerosis:** The criteria was changed to require that the patient has a relapsing form of MS. The criteria that previously required the patient have a diagnosis of multiple sclerosis or has experienced an attack and is at risk of MS. **Conditions Not Recommended for Approval:** The condition of Non-Relapsing Forms of MS was added as an exclusion. A note is provided that an example of a non-relapsing form is primary progressive MS. Regarding Use with Other Disease-Modifying Agents for MS, the examples are now listed as a note with Mavenclad and Mayzent added.	07/17/2019
Annual Revision	The following criteria changes were made: **Conditions Not Recommended for Approval:** Bafiertam, Vumerity, and Zeposia were added to the Note that provides examples of disease-modifying MS agents in which Plegridy should not be used with concurrently.	08/05/2020
Selected Revision	**Multiple Sclerosis:** Examples of relapsing forms of MS were added in a Note. **Conditions Not Recommended for Approval:** Regarding Use with Other Disease-Modifying Agents for MS, Kesimpta was added to the list of examples provided in the Note.	09/09/2020
Selected Revision	New Plegridy products that are administered intramuscularly were added to the policy with the same criteria as those applied to the subcutaneous products. There were no other changes to the criteria.	02/17/2021

MS – Multiple sclerosis.

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Plegridy Prior Authorization Policy

- Plegridy® (peginterferon beta-1a injection for subcutaneous or intramuscular use – Biogen Idec)

REVIEW DATE: 08/05/2020; selected revision 09/09/2020 and 02/17/2021

OVERVIEW

Plegridy, an interferon beta product, is indicated for the treatment of relapsing forms of multiple sclerosis (MS) to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease in adults.[1]

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system that impacts almost 1,000,000 people in the US.[2] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40

years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[3] as well as in 2017.[4] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-4] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Plegridy. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Plegridy as well as the monitoring required for adverse events and long-term efficacy, approval requires Plegridy to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Plegridy is recommended in those who meet the following criteria:

FDA-Approved Indication

3. Multiple Sclerosis. Approve for 3 years if the patient meets the following criteria (A and B):

X) Patient has a relapsing form of multiple sclerosis; AND
Note: Examples of relapsing forms of multiple sclerosis (MS) include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

Y) Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Plegridy is not recommended in the following situations:

34. Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.
Note: Examples of disease modifying agents used for multiple sclerosis include Avonex® (interferon beta-1a injection [intramuscular]), Betaseron®/Extavia® (interferon beta-1b injection), Rebif® (interferon beta-1a injection [subcutaneous]), Copaxone®/Glatopa® (glatiramer acetate injection), Aubagio® (teriflunomide tablets), Gilenya® (fingolimod tablets), Mavenclad® (cladribine tablets), Mayzent® (siponimod tablets), Tecfidera® (dimethyl fumarate delayed-release capsules), Bafiertam® (monomethyl fumarate delayed-release capsules), Vumerity® (diroximel fumarate delayed-release capsules), Zeposia® (ozanimod capsules), Ocrevus® (ocrelizumab injection for intravenous use), Tysabri® (natalizumab injection for intravenous infusion), Lemtrada® (alemtuzumab injection for intravenous use), and Kesimpta® (ofatumumab injection for subcutaneous use).[2] These agents are not indicated for use in combination. Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

35. Non-Relapsing Forms of Multiple Sclerosis.
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis. The efficacy of Plegridy has not been established in patients with multiple sclerosis with non-relapsing forms of multiple sclerosis.[1]

36. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

33. Plegridy® injection for subcutaneous or intramuscular use [prescribing information]. Cambridge, MA: Biogen, Idec; January 2021.
34. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. September 2019. Available at: http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed on September 9, 2020.
35. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
36. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	The following criteria changes were made: **Multiple Sclerosis:** The criteria was changed to require that the patient has a relapsing form of MS. The criteria that previously required the patient have a diagnosis of multiple sclerosis or has experienced an attack and is at risk of MS. **Conditions Not Recommended for Approval:** The condition of Non-Relapsing Forms of MS was added as an exclusion. A note is provided that an example of a non-relapsing form is primary progressive MS. Regarding Use with Other Disease-Modifying Agents for MS, the examples are now listed as a note with Mavenclad and Mayzent added.	07/17/2019
Annual Revision	The following criteria changes were made: **Conditions Not Recommended for Approval:** Bafiertam, Vumerity, and Zeposia were added to the Note that provides examples of disease-modifying MS agents in which Plegridy should not be used with concurrently.	08/05/2020
Selected Revision	**Multiple Sclerosis:** Examples of relapsing forms of MS were added in a Note. **Conditions Not Recommended for Approval:** Regarding Use with Other Disease-Modifying Agents for MS, Kesimpta was added to the list of examples provided in the Note.	09/09/2020
Selected Revision	New Plegridy products that are administered intramuscularly were added to the policy with the same criteria as those applied to the subcutaneous products. There were no other changes to the criteria.	02/17/2021

MS – Multiple sclerosis.

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Vumerity Prior Authorization Policy
- Vumerity® (diroximel fumarate delayed-release capsules – Biogen/Alkermes)

REVIEW DATE: 08/05/2020; selected revision 09/09/2020

OVERVIEW

Vumerity is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive MS in adults.[1]

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[2] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[3] as well as in 2017.[4] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-4] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

Safety

Progressive multifocal leukoencephalopathy has occurred in patients with MS treated with dimethyl fumarate delayed-release capsules, which has the same active metabolite as Vumerity.[1]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Vumerity. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and

diagnosis of patients treated with Vumerity as well as the monitoring required for adverse events and efficacy, approval requires Vumerity to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vumerity is recommended in those who meet the following criteria.

FDA-Approved Indication

1. **Multiple Sclerosis.** Approve for 1 year if the patient meets the following criteria (A and B):
   - **E)** Patient has a relapsing form of multiple sclerosis; AND
     Note: Examples of relapsing forms of multiple sclerosis (MS) include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
   - **F)** Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vumerity is not recommended in the following situations:

174. Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.
Note: Examples of disease modifying agents used for multiple sclerosis include Aubagio® (teriflunomide tablets), Avonex® (interferon beta 1a injection [intramuscular]), Betaseron®/Extavia® (interferon beta-1b injection), Rebif® (interferon beta-1a injection [subcutaneous]), Copaxone®/Glatopa® (glatiramer acetate injection), Plegridy® (peginterferon beta-1a injection), Gilenya® (fingolimod tablets), Mavenclad® (cladribine tablets), Mayzent® (siponomid tablets), Tecfidera® (dimethyl fumarate delayed-release capsules), Bafiertam® (monomethyl fumarate delayed-release capsules), Zeposia® (ozanimod capsules), Ocrevus® (ocrelizumab injection for intravenous use), Tysabri® (natalizumab injection for intravenous infusion), Lemtrada® (alemtuzumab injection for intravenous use), and Kesimpta® (ofatumumab injection for subcutaneous use).[2] These agents are not indicated for use in combination. Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

175. Non-Relapsing Forms of Multiple Sclerosis.
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis. The efficacy of Vumerity has not been established in patients with multiple sclerosis with non-relapsing forms of multiple sclerosis.[1]

176. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

214. Vumerity® delayed-release capsules [prescribing information]. Cambridge, MA and Waltham, MA: Biogen and Alkermes; March 2020.
215. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. September 2019. Available at: http://www.nationalmssociety.org/getmedia/5ca284d3-fc7c-4ba5-b005-ab537d495c3c/DMT_Consensus_MS_Coalition_color. Accessed on September 9, 2020.
216. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.

217. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	---	11/06/2019
Early Annual Revision	The following criteria changes were made: **Conditions Not Recommended for Approval:** Bafiertam and Zeposia were added to the Note that provides examples of disease-modifying MS agents in which Aubagio should not be used with concurrently.	08/05/2020
Selected Revision	**Multiple Sclerosis:** Examples of relapsing forms of MS were added in a Note. **Conditions Not Recommended for Approval:** Regarding Use with Other Disease-Modifying Agents for MS, Kesimpta was added to the list of examples provided in the Note.	09/09/2020

MS – Multiple sclerosis.

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Zeposia Prior Authorization Policy

- Zeposia® (ozanimod capsules – Celegene)

REVIEW DATE: 08/05/2020; selected revision 09/09/2020

OVERVIEW

Zeposia, a sphingosine 1-phosphate receptor modulator, is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease in adults.[1]

Disease Overview

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.[2] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[3] as well as in 2017.[4] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-4] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Guidelines

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

Safety

Various assessments are required prior to the first dose of Zeposia (e.g., complete blood count, cardiac evaluation).[1] The most common adverse events with Zeposia include upper respiratory tract infection, hepatic transaminase elevations, orthostatic hypotension, urinary tract infection, back pain, and hypertension. Zeposia has Warnings/Precautions regarding infections, macular edema, bradyarrhythmias and atrioventricular conduction delays, respiratory effects, liver injury, increased blood pressure, and respiratory effects. Due to the time it takes to eliminate the drug from the body after cessation of treatment, the potential risk of the fetus may persist, therefore, women of childbearing potential should use effective contraception to avoid pregnancy during and for up to 3 months after cessation of Zeposia therapy.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Zeposia. All approvals are provided for the duration cited below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zeposia as well as the monitoring required for adverse events and long-term efficacy, approval requires Zeposia to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zeposia is recommended in those who meet the following criteria:

FDA-Approved Indications

5. Multiple Sclerosis. Approve for 1 year if the patient meets the following criteria (A and B):

- **A)** Patient has a relapsing form of multiple sclerosis; AND
  Note: Examples of relapsing forms of multiple sclerosis (MS) include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
- **B)** Medication is prescribed by or in consultation with neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zeposia is not recommended in the following situations:

177. Current Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.

Note: Examples of disease-modifying agents used for multiple sclerosis include Avonex® (interferon beta 1a injection [intramuscular]), Betaseron®/Extavia® (interferon beta-1b injection), Rebif® (interferon beta-1a injection [subcutaneous]), Copaxone®/Glatopa® (glatiramer acetate injection), Plegridy® (peginterferon beta-1a injection), Aubagio® (teriflunomide tablets), Gilenya® (fingolimod tablets), Mavenclad® (cladribine tablets), Mayzent® (siponimod tablets), Tecfidera® (dimethyl fumarate delayed-release capsules), Vumerity® (diroximel fumarate delayed-release capsules), Bafiertam® (monomethyl fumarate delayed-release capsules), Ocrevus® (ocrelizumab injection for intravenous use), Tysabri® (natalizumab injection for intravenous infusion), Lemtrada® (alemtuzumab

injection for intravenous use), and Kesimpta® (ofatumumab injection for subcutaneous use).[2] These agents are not indicated for use in combination. Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

178. Non-Relapsing Forms of Multiple Sclerosis.
Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis. The efficacy of Zeposia has not been established in patients with multiple sclerosis with non-relapsing forms of the disease.[1]

179. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/15/2020
Early Annual Revision	The following criteria changes were made: **Conditions Not Recommended for Approval:** Bafiertam was added to the Note that provides examples of disease-modifying MS agents in which Zeposia should not be used with concurrently.	08/05/2020
Selected Revision	**Multiple Sclerosis:** Examples of relapsing forms of MS were added in a Note. **Conditions Not Recommended for Approval:** Regarding Use with Other Disease-Modifying Agents for MS, Kesimpta was added to the list of examples provided in the Note.	09/09/2020

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis and Crohn's Disease – Tysabri Prior Authorization Policy
- Tysabri® (natalizumab injection for intravenous use – Biogen)

REVIEW DATE: 11/11/2020

OVERVIEW

Tysabri, an integrin receptor antagonist, is indicated for the treatment of:[1]
- Relapsing forms of **multiple sclerosis (MS)** to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease in adults as monotherapy in adults.[1]
- **Crohn's disease**, inducing and maintaining clinical response and remission in adults with moderately to severely active disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional Crohn's disease therapies and inhibitors of tumor necrosis factor (TNF)-α.

Tysabri increases the risk of progressive multifocal leukoencephalopathy (PML).[1] When initiating and continuing treatment with Tysabri in patients with MS, physicians should consider whether the expected

benefit of Tysabri is sufficient to offset the risks. Tysabri should not be used in combination with immunosuppressants (e.g., azathioprine, 6-mercaptopurine, cyclosporine, methotrexate) or inhibitors of TNFα. The safety and effectiveness in pediatric patients with MS or Crohn's disease below the age of 18 years of age have not been established.

Disease Overview

Multiple Sclerosis (MS)

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system that impacts almost 1,000,000 people in the US.[2] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[3] as well as in 2017.[4] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-4] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria.

Crohn's Disease

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract.[6] The prevalence has been increasing worldwide.[7] Common symptoms of Crohn's disease include abdominal pain, diarrhea, fatigue, weight loss, fever, anemia, and recurrent fistulas. Adults with Crohn's disease may be at risk of bone fractures, as well as thromboembolism. Other extraintestinal manifestations may occur (e.g., primary sclerosing cholangitis). Younger patients may experience growth failure.[6,7] The chronic intestinal inflammation over time leads to intestinal complications such as strictures, fistulas, and abscesses. Only 20% to 30% of patients with Crohn's disease will have a nonprogressive or indolent course. Therefore, it is appropriate to identify therapies that will achieve adequate control for the patient. Many different therapies are available including corticosteroids, immunomodulators (e.g., azathiopurine, 6-mercaptopurine), and anti-TNF agents (e.g., infliximab products, adalimumab products, Cimzia® [certolizumab pegol injection for subcutaneous use]).

Guidelines

A practice guideline recommendation regarding disease-modifying agents for adults with MS from the American Academy of Neurology (2018) states to consider Tysabri for patients with MS who have highly active disease.[5]

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various disease classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

The American College of Gastroenterology has guidelines on management of Crohn's disease in adults (2018).[7] Anti-TNF agents (e.g., infliximab products, adalimumab products, Cimzia® [certolizumab pegol injection for subcutaneous use]) should be used to treat Crohn's disease that is resistant to treatment with corticosteroids, thiopurines or methotrexate. For patients with moderately to severely active Crohn's

disease and objective evidence of active disease, anti-integrin therapy (with Entyvio® [vedolizumab injection for intravenous use) with or without an immunomodulator is more effective than placebo and should be considered for use for induction of symptomatic remission in patients with Crohn's disease. Tysabri is more effective than placebo and should be considered to be used for induction of symptomatic response and remission in patients with active Crohn's disease (strong recommendation; high level of evidence). Tysabri should be used for maintenance of Tysabri-induced remission of Crohn's disease only if serum antibody to John Cunningham virus is negative. Stelara® (ustekinumab injection for subcutaneous or intravenous use) should be given for moderate to severe Crohn's disease patients who failed treatment with corticosteroids, thiopurines, methotrexate, or anti-TNF inhibitors or who have had no prior exposure to anti-TNF inhibitors.

Safety

Tysabri has a Boxed Warning regarding the risk of PML. Tysabri is available only through a special restricted distribution Risk Evaluation and Mitigation Strategy (REMS) program called the TOUCH® Prescribing Program.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tysabri. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tysabri as well as the monitoring required for adverse events and long-term efficacy, approval requires Tysabri to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Tysabri at initiation for MS as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes magnetic resonance imaging (MRI) reports, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tysabri injection is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Multiple Sclerosis.** Approve for 1 year if the patient meets one of the following criteria (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets all of the following criteria (i, ii, iii and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has a relapsing form of multiple sclerosis; AND
       Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.
     - **iii.** Patient meets one of the following (a or b):
       - **a)** According to the prescriber the patient has experienced inadequate efficacy or significant intolerance to one disease-modifying agent used for MS; OR
         Note: Examples include Avonex® (interferon beta-1a injection [intramuscular]), Rebif® (interferon beta-1a injection [subcutaneous]), Betaseron®/Extavia® (interferon beta-1b injection), glatiramer acetate injection (Copaxone®/Glatopa®, generic), Plegridy® (peginterferon beta-1a injection), Gilenya® (fingolimod capsules), Aubagio®

(teriflunomide tablets), Mavenclad® (cladribine tablets), Mayzent® (siponimod tablets), Vumerity® (diroximel fumarate delayed-release capsules), Ocrevus® (ocrelizumab injection for intravenous use), Bafiertam™ (monomethyl fumarate delayed-release capsules), dimethyl fumarate delayed-release capsules (Tecfidera®, generic), Zeposia® (ozanimod capsules), Kesimpta® (ofatumumab injection for subcutaneous use), and Lemtrada® (alemtuzumab injection for intravenous use).

b) According to the prescriber the patient has highly-active or aggressive multiple sclerosis by meeting one of the following [(1), (2), (3), or (4)]:

(5) Patient has demonstrated rapidly-advancing deterioration(s) in physical functioning (e.g., loss of mobility/or lower levels of ambulation, severe changes in strength or coordination) **[documentation required]**; OR

(6) Disabling relapse(s) with suboptimal response to systemic corticosteroids **[documentation required]**; OR

(7) Magnetic resonance imaging [MRI] findings suggest highly-active or aggressive multiple sclerosis (e.g., new, enlarging, or a high burden of T2 lesions or gadolinium-enhancing lesions) **[documentation required]**; OR

(8) Manifestations of multiple sclerosis-related cognitive impairment **[documentation required]**; AND

iv. Medication is prescribed by or in consultation with a physician who specializes in the treatment of multiple sclerosis and/or a neurologist; AND

B) Patient is currently receiving Tysabri. Approve for 1 year if the patient meets all of the following criteria (i, ii, and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient has a relapsing form of multiple sclerosis; AND
Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

iii. Medication is prescribed by or in consultation with a physician who specializes in the treatment of multiple sclerosis and/or a neurologist.

2. Crohn's Disease. Approve for the duration noted below if the patient meets one of the following criteria (A OR B):

A) Initial Therapy. Approve for 3 months if the patient meets all of the following criteria (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Patient has moderately to severely active Crohn's disease; AND

iii. Patient has tried at least two biologics for Crohn's disease; AND
Note: Examples include an adalimumab product, Cimzia (certolizumab pegol for SC injection), an infliximab product, Entyvio (vedolizumab injection for IV use), or Stelara (ustekinzumab for SC injection or for IV infusion).

iv. Medication is prescribed by or in consultation with a gastroenterologist; OR

B) Patient is Currently Receiving Tysabri. Approve for 1 year if the patient meets all of the following criteria (i, ii and iii):

i. Patient is ≥ 18 years of age; AND

ii. Patient has had a response as determined by the prescriber; AND
Note: Examples of a response are reduced number of liquid/soft stools, reduced abdominal pain, and less use of antidiarrheal agents.

iii. Medication is prescribed by or in consultation with a gastroenterologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tysabri is not recommended in the following situations:

1. **Concurrent Use with an Immunosuppressant Agent in Patients with Crohn's Disease.** Ordinarily, patients who are receiving chronic immunosuppressant or immunomodulatory therapy or who have systemic medical conditions resulting in significantly compromised immune function should not take Tysabri.[1]
   Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, methotrexate, an infliximab product, an adalimumab product, Cimzia, Entyvio and Stelara.

2. **Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis (MS).** Tysabri is only indicated as monotherapy due to an increased risk of PML.[1]
   Note: Examples include Avonex® (interferon beta-1a injection [intramuscular]), Rebif® (interferon beta-1a injection [subcutaneous]), Betaseron®/Extavia® (interferon beta-1b injection), glatiramer acetate injection (Copaxone®/Glatopa®, generic), Plegridy® (peginterferon beta-1a injection), Gilenya® (fingolimod capsules), Aubagio® (teriflunomide tablets), Mavenclad® (cladribine tablets), Mayzent® (siponimod tablets), Vumerity® (diroximel fumarate delayed-release capsules), Ocrevus® (ocrelizumab injection for intravenous use), Bafiertam™ (monomethyl fumarate delayed-release capsules), dimethyl fumarate delayed-release capsules (Tecfidera®, generic), Zeposia® (ozanimod capsules), Kesimpta® (ofatumumab injection for subcutaneous use), and Lemtrada® (alemtuzumab injection for intravenous use).

3. **Non-Relapsing Forms of Multiple Sclerosis.** The safety and efficacy of Tysabri have not been established in patients with primary progressive multiple sclerosis.
   Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.

4. **Ulcerative Colitis.** Efficacy data with use of Tysabri are limited.[8]

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	The following criteria changes were made: **5. Multiple Sclerosis:** The notation of "Relapsing Forms" was removed from the stated indication. Criteria were revised such that the example of relapsing forms of MS were	11/13/2019

	removed. The word "prescriber" replaced the phrase "prescribing physician" in applicable criteria. Vumerity and glatiramer acetate were added as medication alternatives that count toward the requirement of a trial of one disease-modifying agent used for MS. 6. **Crohn's Disease:** Regarding the requirement that patients have moderate or severely active Crohn's disease, patients no longer are required to have "evidence of inflammation, that is C-reactive protein", as this is no longer recommended in related guidelines. The word "prescriber" replaced the phrase "prescribing physician" in applicable criteria. 7. **Conditions Not Recommended for Approval:** "Children with MS or Crohn's Disease" was removed as this is duplicative to the age requirement in the approval criteria. Regarding "Concurrent Use with Other Disease-Modifying Agents Used for MS", the examples of glatiramer acetate injection, Vumerity, Mavenclad, and Mayzent were added. The condition that stated "Primary Progressive (Chronic Progressive MS)" was changed to state "Non-Relapsing Forms of MS" with a note that an example is Primary Progressive MS. The condition of "Immune Compromised Patients with MS or Crohn's Disease" was removed.	
Update	02/07/2020: No criteria changes. The title Crohn's Disease was added to the header on the name of the policy.	--
Annual Revision	The following changes were made: 5. **Multiple Sclerosis:** For the criteria that requires that the patient try two other disease-modifying medications for MS, the wording regarding this trial was changed from and "has had an inadequate response or is unable to tolerate" to "has experienced inadequate efficacy or significant intolerance." Additional agents were added as examples of MS disease-modifying therapies in the Note. A Note was added after the requirement that the patient have a relapsing form of MS that examples of relapsing forms of MS include clinically isolated syndrome, relapsing remitting disease and active secondary progressive disease. 6. **Crohn's Disease:** Examples of a response for patients currently receiving Tysabri was removed from the criteria and placed in a Note. 7. **Conditions Not Recommended for Approval:** For the criteria regarding "Concurrent Use with Other Disease-Modifying Agents Used for MS", examples of agents were added to the Note.	11/11/2020

MS – Multiple sclerosis.

PRIOR AUTHORIZATION POLICY

POLICY: Muscular Dystrophy – Amondys 45 Prior Authorization Policy

- Amondys 45™ (casimersen intravenous infusion – Sarepta)

REVIEW DATE: 02/26/2021

OVERVIEW

Amondys 45, an antisense oligonucleotide, is indicated for the treatment of **Duchenne muscular dystrophy** (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping.[1] This indication was granted accelerated approval based on an increase in dystrophin in skeletal muscle observed in patients treated with Amondys 45. The prescribing information notes that continued FDA-approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.

Amondys 45 is an antisense oligonucleotide designed to bind to exon 45 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 45 skipping. These patients represent up to 8% of all patients with DMD.[2] This genetic manipulation intends to restore the reading frame of the resulting mRNA. The result would be production of a shortened, but partially functional dystrophin protein as seen in less severe forms of muscular dystrophy (e.g., Becker muscular dystrophy).

Guidelines

Amondys 45 is not addressed in guidelines for DMD. There are guidelines for the diagnosis and management of DMD available from the DMD Care Considerations Working Group (2018).[3] Genetic testing for a DMD mutation in a blood sample is always required. By fully characterizing the mutation, the predicted effect on the reading frame can be identified, which is the major determinant of phenotype and will determine eligibility for mutation-specific clinical trials. In patients with no mutation identified but with signs/symptoms of DMD, a muscle biopsy is clinically indicated. Glucocorticoids slow decline in muscle strength and function in DMD. Use of corticosteroids reduces the risk of scoliosis and stabilizes pulmonary function. Continued treatment after the patient loses ambulation provides a reduction in the risk of progressive scoliosis and stabilization of pulmonary function tests. Therefore, glucocorticoids should be considered for all patients with DMD. Exondys 51 (eteplirsen intravenous infusion) is mentioned as an emerging product, approved by an accelerated pathway for those with a mutation in the dystrophin gene amenable to exon 51 skipping.

POLICY STATEMENT

The prescribing information for Amondys 45 states that approval is based on dystrophin production in a limited number of patients (n = 27 treated with Amondys 45) with DMD, but continued approval may be contingent upon a confirmatory trial. Due to inadequate clinical efficacy data, **approval is not recommended** for Amondys 45.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Amondys 45 is not recommended in the following situations:

1. **Duchenne Muscular Dystrophy (DMD).** Due to inadequate clinical efficacy data, approval is not recommended. A systemic review and meta-analysis of other exon skipping therapies (i.e., Exondys 51, drisapersen) does not show benefit of these therapies for DMD.[4] The prescribing information notes that continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.[1] FDA has required a post-marketing trial to verify clinical efficacy of Amondys 45. Thus, patients are still being recruited for the pivotal Phase III ESSENCE study, to further evaluate safety and efficacy in ambulatory boys with DMD.[5]

   Amondys 45 is under evaluation in one ongoing, Phase III pivotal study (ESSENCE) in patients with DMD amenable to exon 45 skipping.[1] The primary endpoint is the effect of Amondys 45 change from baseline in the total distance walked during the 6-Minute Walk Test (6MWT) at Week 96.[5] Functional outcomes were among the secondary endpoints. In an interim analysis from 43 evaluable patients (n = 27 treated with Amondys 45; n = 16 treated with placebo), the proportion of normal dystrophin protein level was higher at Week 48 with Amondys 45 (1.74% of normal at Week 48 vs. 0.93% of normal at baseline) vs. placebo (0.76% of normal at Week 48 vs. 0.54% of normal at baseline) [P = 0.004 for Amondys 45 vs. placebo).[1] Results from the primary endpoint (6MWT) and functional outcomes have not been reported.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY
Type of Revision	Summary of Changes	Review Date
New Policy	--	02/26/2021

PRIOR AUTHORIZATION POLICY

POLICY: Muscular Dystrophy – Emflaza Prior Authorization Policy
- Emflaza™ (deflazacort tablets and oral suspension – PTC Therapeutics, Inc.)

REVIEW DATE: 01/20/2021

OVERVIEW

Emflaza is a corticosteroid indicated for the treatment of patients ≥ 2 years of age with **Duchenne muscular dystrophy** (DMD).[1] The efficacy and safety of Emflaza have not been established in patients < 2 years of age.

Disease Overview

DMD is an X-linked recessive disease affecting 1 in 3,600 to 6,000 newborn male infants.[2] The disease is attributed to large frame-shift deletions in the DMD gene (chromosome Xp21) which lead to loss of a structural protein of muscle cells (dystrophin).[3] Females carriers are usually asymptomatic but some may show mild symptoms.[2] Most patients present with symptoms of DMD between the ages of 3 and 5 years. There are wide variances in how quickly DMD progresses, but without intervention death is at approximately 19 years of age.[2-3] With respiratory, cardiac, orthopedic and rehabilitative interventions and use of corticosteroids, children born today can have a life expectancy of up to 40 years.

Clinical Efficacy

The efficacy and safety of Emflaza were established in two pivotal trials in boys with DMD who were ≥ 5 years of age.[4-5] In one study, treatment consisted of Emflaza 0.9 mg/kg/day, Emflaza 1.2 mg/kg/day, or prednisone 0.75 mg/kg/day (n = 196).[4] The primary efficacy analysis, mean change from baseline to Week 12 in average muscle strength (assessed by modified Medical Research Council [MRC]), demonstrated a significant least squares (LS) mean difference in favor of active treatment vs. placebo: Emflaza 0.9 mg/kg/day (0.25 vs. -0.1, P = 0.17), Emflaza 1.2 mg/kg/day (0.36 vs. -0.1, P = 0.0003), and prednisone 0.75 mg/kg/day (0.37 vs. -0.1, P = 0.0002). Adverse events (AEs) differed between prednisone and Emflaza treatment groups. Cushingoid appearance (69.4%), erythema (41.8%), and hirsutism (39.3%) were observed in a numerically greater proportion of patients in the prednisone group compared with either dose of Emflaza. Central obesity was reported in a statistically significant greater proportion of patients treated with prednisone vs. Emflaza. Psychiatric AEs were generally reported at a higher rate in the prednisone group compared with both Emflaza groups.

Guidelines

There are guidelines for the diagnosis and management of DMD available from the DMD Care Considerations Working Group (updated 2018).[6] Dystrophin gene deletion and duplication testing are usually the first test done to confirm a diagnosis of DMD. If deletion/duplication testing is negative, dystrophin gene sequencing is done to look for remaining types of mutations. If generic testing does not confirm a diagnosis of DMD, then a muscle biopsy should be performed to test for the presence of dystrophin protein. These guidelines additionally discuss the benefits of glucocorticoids in patients with DMD. These benefits include the loss of ambulation at a later age, preservation of upper limb and respiratory function, and avoidance of scoliosis surgery. Although the benefits of glucocorticoids are well established, based on available data, there is uncertainty about which specific products and doses are best.[6]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Emflaza. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Emflaza as well as the monitoring required for adverse events and long-term efficacy, approval requires Emflaza to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Emflaza as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Emflaza is recommended in those who meet the following criteria:

FDA-Approved Indications

30. Duchenne Muscular Dystrophy (DMD). Approve for 1 year if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve if the patient meets the following criteria (i, ii, and iii):

i. Patient is 2 years of age and older; AND

ii. Patient meets ONE of the following conditions (a or b):

a) Patient has tried prednisone or prednisolone for ≥ 6 months **[documentation required]** AND according to the prescriber, the patient has had at least one of the following significant intolerable adverse effects (AEs) [1, 2, 3, or 4]:

1) Cushingoid appearance **[documentation required]**; OR

2) Central (truncal) obesity **[documentation required]**; OR

3) Undesirable weight gain defined as ≥ 10% of body weight gain increase over a 6-month period **[documentation required]**; OR

4) Diabetes and/or hypertension that is difficult to manage according to the prescriber **[documentation required]**; OR

b) According to the prescriber, the patient has experienced a severe behavioral adverse event (AE) while on prednisone or prednisolone therapy that has or would require a prednisone or prednisolone dose reduction **[documentation required]**.

iii. The medication is prescribed by or in consultation with a physician who specializes in the treatment of Duchenne muscular dystrophy and/or neuromuscular disorders.

B) Patient is currently receiving Emflaza. Approve if the patient meets the following criteria (i, ii, and iii):

i. Patient has tried prednisone or prednisolone **[documentation required]**; AND

ii. According to the prescriber, the patient has responded to or continues to have improvement or benefit from Emflaza therapy **[documentation required]**; AND

Note: Examples of improvement or benefit from Emflaza therapy would include improvements in motor function (time from supine to standing, time to climb four stairs, time to run or walk 30 feet), improvement in muscle strength, improve pulmonary function, etc.

iii. The medication is prescribed by or in consultation with a physician who specializes in the treatment of Duchenne muscular dystrophy and/or neuromuscular disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Emflaza is not recommended in the following situations:

180. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes	3/13/2019
Selected Revision	For Duchenne Muscular Dystrophy, the FDA-approved age for use was updated to patients 2 years of age and older. Previously the approved age was ≥ to 5 years of age.	6/26/2019
Annual Revision	Throughout the policy, updated prescribing physician to prescriber	3/11/2020
Early Annual Revision	Throughout the policy, prednisolone was added in places referencing prednisone. Added continuation criteria for patients currently receiving Emflaza: Continuation criteria requires a trial of prednisone or prednisolone; documentation of response; and prescribing by or in consultation with a physician who specializes in the treatment of Duchenne muscular dystrophy and/or neuromuscular disorders.	01/20/2021

PRIOR AUTHORIZATION POLICY

POLICY: Muscular Dystrophy – Exondys 51™ (eteplirsen intravenous infusion – Sarepta)

DATE REVIEWED: 04/15/2020

OVERVIEW

Exondys 51 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.[1] Exondys 51 was approved for this indication under accelerated approval based on an increase in dystrophin observed in the skeletal muscle of some patients who received the drug. However, a clinical benefit of Exondys has not been established. The prescribing information notes that continued FDA-approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Disease Overview

DMD is an X-linked recessive disease affecting 1 in 3,600 to 6,000 newborn male infants.[2] The disease is attributed to large frame-shift deletions in the DMD gene (chromosome Xp21) which lead to loss of a structural protein of muscle cells (dystrophin).[3] Over 4,700 mutations on the DMD gene have been identified which lead to a deficiency in production of dystrophin.[2] Therefore, the type of mutation and its effect on the production of dystrophin accounts for the variable phenotypic expression.[4] Females carriers are usually asymptomatic but some may show mild symptoms.[2] There are wide variances in how quickly DMD progresses, but without intervention death is at approximately 19 years of age.[2-4] With respiratory, cardiac, orthopedic and rehabilitative interventions and use of corticosteroids, children born today can have a life expectancy of up to 40 years.

Exondys 51 is an antisense oligonucleotide designed to bind to exon 51 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 51 skipping.[1] These patients represent approximately 13% of all patients with DMD.[5] This genetic manipulation intends to restore the reading frame of the resulting mRNA. The result would be production of a shortened, but partially functional dystrophin protein as seen in less severe forms of muscular dystrophy (e.g., Becker muscular dystrophy).

Guidelines

There are guidelines for the diagnosis and management of DMD available from the DMD Care Considerations Working Group (2018).[4] Genetic testing for a DMD mutation in a blood sample is always required. By fully characterizing the mutation, the predicted effect on the reading frame can be identified, which is the major determinant of phenotype and will determine eligibility for mutation-specific clinical trials. In patients with no mutation identified but with signs/symptoms of DMD, a muscle biopsy is clinically indicated. Glucocorticoids slow decline in muscle strength and function in DMD. Use of corticosteroids reduces the risk of scoliosis and stabilizes pulmonary function. Continued treatment after the patient loses ambulation provides a reduction in the risk of progressive scoliosis and stabilization of pulmonary function tests. Therefore, glucocorticoids should be considered for all patients with DMD. Exondys 51 is mentioned as an emerging product, approved by an accelerated pathway for those with a mutation in the dystrophin gene amenable to exon 51 skipping.

POLICY STATEMENT

The prescribing information for Exondys 51 states that a clinical benefit has not been established. Due to the lack of clinical efficacy data, **approval is not recommended** for Exondys 51.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Exondys 51 has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

3. **Duchenne Muscular Dystrophy (DMD).** Due to the lack of clinical efficacy data, approval is not recommended for Exondys 51. The prescribing information for Exondys 51 states that a clinical benefit has not been established.[1] Furthermore, a systemic review and meta-analysis does not show benefit of exon-skipping therapies for DMD.[10] FDA has required a randomized, controlled trial evaluation post-marketing to establish efficacy of Exondys 51. Results are expected in 2021.

   The efficacy of Exondys 51 was evaluated in open-label studies in patients with DMD that is amenable to exon 51 skipping.[1,6-9] One study (n = 12) assessed the effect of Exondys 51 on dystrophin and the potential clinical benefit; however, there was insufficient information on dystrophin levels prior to treatment so it is not possible to estimate a treatment effect on dystrophin levels. The adjusted mean change in the 6-minute walk test (6MWT) from baseline to Week 24 was -25.8 (±30.6) meters for placebo; -128.2 (±31.6) meters for Exondys 51, 30 mg/kg; and -0.3 (±31.2) meters for Exondys 51, 50 mg/kg. An extension of this study evaluated the same patients and compared disease progression with matched historical controls; at Month 36 the difference in 6MWT distance for Exondys 51 vs. historical control was 121 meters in favor of the Exondys 51 cohort (P = 0.028). Over 36 months, ambulation

was lost in 16.7% of patients (n = 2/12) treated with Exondys 51 vs. 46.2% of patients (n = 6/13) in the historical control cohort. The average dystrophin protein level after 180 weeks of treatment with Exondys 51 was 0.93% of the dystrophin level in healthy subjects. But because there was insufficient information on baseline dystrophin levels prior to treatment, it is not possible to estimate a treatment effect. Following 240 weeks of treatment, the percent predicted forced vital capacity (FVC%p) was a decrease of 2.3% per year with Exondys 51 compared with a decrease of 4.1% in a natural history cohort.[11] In patients treated with Exondys 51, the percent predicted maximum inspiratory pressure (MIP%p) decreased by 1% per year, and the percent predicted maximum expiratory pressure (MEP%p) decreased by 2.6% per year. However, MIP and MEP were not assessed in the natural history cohort. Another study included 12 new patients with DMD and reports only on the effect of Exondys 51 on dystrophin levels; further clinical efficacy data are not yet available for these 12 patients.[7-9] After 48 weeks of treatment with Exondys 51 the dystrophin level was 0.44% ± 0.43% of the dystrophin level in healthy subjects ($P < 0.05$). The median increase after 48 weeks was 0.1%.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual revision	No changes to criteria.	10/10/2018
Early annual revision	No changes to criteria.	04/10/2019
Annual revision	No changes to criteria	04/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Muscular Dystrophy – Viltepso Prior Authorization Policy
- Viltepso™ (viltolarsen for intravenous injection)

REVIEW DATE: 08/19/2020

OVERVIEW

Viltepso, an antisense oligonucleotide, is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.[1] This indication was granted accelerated approval based on an increase in dystrophin in skeletal muscle observed in patients treated with Viltepso. The prescribing information notes that continued FDA-approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.

Viltepso is an antisense oligonucleotide designed to bind to exon 53 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 53 skipping.[1] These patients represent up to 10% of all patients with DMD.[2] This genetic manipulation intends to restore the reading frame of the resulting mRNA. The result would be production of a shortened, but partially functional dystrophin protein as seen in less severe forms of muscular dystrophy (e.g., Becker muscular dystrophy). Of note, the reading frame of certain deletions (e.g., exon 52 deletions) can be restored by skipping either exon 51 or exon 53.[3] Approximately 8% of mutations are amenable to skipping exon 53 with Viltepso but are not amenable to skipping of exon 51.

Guidelines

Viltepso and other exon 53 skipping therapies are not addressed in guidelines for DMD. There are guidelines for the diagnosis and management of DMD available from the DMD Care Considerations Working Group (2018).[4] Genetic testing for a DMD mutation in a blood sample is always required. By fully characterizing the mutation, the predicted effect on the reading frame can be identified, which is the major determinant of phenotype and will determine eligibility for mutation-specific clinical trials. In patients with no mutation identified but with signs/symptoms of DMD, a muscle biopsy is clinically indicated. Glucocorticoids slow decline in muscle strength and function in DMD. Use of corticosteroids reduces the risk of scoliosis and stabilizes pulmonary function. Continued treatment after the patient loses ambulation provides a reduction in the risk of progressive scoliosis and stabilization of pulmonary function

tests. Therefore, glucocorticoids should be considered for all patients with DMD. Exondys 51 (eteplirsen intravenous infusion) is mentioned as an emerging product, approved by an accelerated pathway for those with a mutation in the dystrophin gene amenable to exon 51 skipping.

POLICY STATEMENT

The prescribing information for Viltepso states that approval is based on dystrophin production in a limited number of patients (n = 8 treated with the approved dose) with DMD, but approval may be contingent upon a confirmatory trial. Due to inadequate clinical efficacy data, **approval is not recommended** for Viltepso.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Viltepso is not recommended in the following situations:

5. **Duchenne Muscular Dystrophy (DMD).** Due to inadequate clinical efficacy data, approval is not recommended for Viltepso. A systemic review and meta-analysis of other exon skipping therapies (i.e., Exondys 51, drisapersen) does not show benefit of these therapies for DMD.[5] The prescribing information notes that continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.[1] FDA has required a post-marketing trial to verify clinical efficacy of Viltepso. Thus, patients are being recruited for the Phase III RACER53 study, to further evaluate safety and efficacy of Viltepso in 74 ambulatory boys with DMD.

   Viltepso is under evaluation in one ongoing Phase II pivotal study in patients with DMD amenable to exon 53 skipping.[6] The primary endpoint is the effect of Viltepso on dystrophin as a surrogate outcome marker. Functional outcomes were among the secondary endpoints and were compared with a natural history cohort controlled for age, functional status, geographic location, and glucocorticoid treatment status. In this pivotal study (n = 16), the proportion of normal dystrophin protein level was higher at Week 25 (0.6% of normal at baseline vs. 5.9% of normal at Week 24 biopsy). The change from baseline in some functional outcomes were significantly improved with Viltepso vs. the natural history cohort (time to run walk 10 meters [0.23 meters/second vs. -0.04 meters/second], time to stand from supine [-0.19 seconds vs. 0.66 seconds], and distance on the 6-minute walk test [28.9 meters vs. -65.3 meters]). However, velocity in the time to stand from supine test, time to climb 4 stairs test, North Star Ambulatory Assessment test, and measures of muscle strength by isometric testing were not significantly different from the control group.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/19/2020

PRIOR AUTHORIZATION POLICY

POLICY: Muscular Dystrophy – Vyondys 53 Prior Authorization Policy
- Vyondys 53™ (golodirsen intravenous infusion – Sarepta)

REVIEW DATE: 12/16/2020

OVERVIEW

Vyondys 53 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.[1] Vyondys 53 was approved for this indication under accelerated approval based on an increase in dystrophin observed in the skeletal muscle of patients who received the drug. The prescribing information notes that continued FDA-approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

Disease Overview

DMD is an X-linked recessive disease affecting 1 in 3,600 to 6,000 newborn male infants.[2] The disease is attributed to large frame-shift deletions in the DMD gene (chromosome Xp21) which lead to loss of a structural protein of muscle cells (dystrophin).[3] Over 4,700 mutations on the DMD gene have been identified which lead to a deficiency in production of dystrophin.[2] Therefore, the type of mutation and its effect on the production of dystrophin accounts for the variable phenotypic expression.[4] Females carriers are usually asymptomatic but some may show mild symptoms.[2] There are wide variances in how quickly DMD progresses, but without intervention death is at approximately 19 years of age.[2-4] With respiratory, cardiac, orthopedic and rehabilitative interventions, and use of corticosteroids, children born today can have a life expectancy of up to 40 years.

Vyondys 53 is an antisense oligonucleotide designed to bind to exon 53 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 53 skipping.[1] These patients represent up to 10% of all patients with DMD.[5] This genetic manipulation intends to restore the reading frame of the resulting mRNA. The result would be production of a shortened, but partially functional dystrophin protein as seen in less severe forms of muscular dystrophy (e.g., Becker muscular dystrophy). Of note, the reading frame of certain deletions (e.g., exon 52 deletions) can be restored by skipping either exon 51 or exon 53.[6] Approximately 8% of mutations are amenable to skipping exon 53 with Vyondys 53 but are not amenable to skipping of exon 51.

Guidelines

There are guidelines for the diagnosis and management of DMD available from the DMD Care Considerations Working Group (2018).[4] Genetic testing for a DMD mutation in a blood sample is always required. By fully characterizing the mutation, the predicted effect on the reading frame can be identified,

which is the major determinant of phenotype and will determine eligibility for mutation-specific clinical trials. In patients with no mutation identified but with signs/symptoms of DMD, a muscle biopsy is clinically indicated. Glucocorticoids slow decline in muscle strength and function in DMD. Use of corticosteroids reduces the risk of scoliosis and stabilizes pulmonary function. Continued treatment after the patient loses ambulation provides a reduction in the risk of progressive scoliosis and stabilization of pulmonary function tests. Therefore, glucocorticoids should be considered for all patients with DMD. Exondys 51 (eteplirsen intravenous infusion) is mentioned as an emerging product, approved by an accelerated pathway for those with a mutation in the dystrophin gene amenable to exon 51 skipping. However, these guidelines do not specifically address exon 53 skipping or mention Vyondys 53 in the guidelines.

POLICY STATEMENT

The prescribing information for Vyondys 53 states that approval is based on dystrophin production in a limited number of patients (n = 25) with DMD, but approval may be contingent upon a confirmatory trial. Due to inadequate clinical efficacy data, **approval is not recommended** for Vyondys 53.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Vyondys 53 has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

7. **Duchenne Muscular Dystrophy (DMD).** Due to inadequate clinical efficacy data, approval is not recommended for Vyondys 53. A systemic review and meta-analysis of other exon skipping therapies (i.e., Exondys 51, drisapersen) does not show benefit of these therapies for DMD.[9] The prescribing information notes that continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.[1] FDA has required a post-marketing trial to verify clinical efficacy of Vyondys 53.

   The efficacy of Vyondys 53 was evaluated in one unpublished, open-label study in patients with DMD that is amenable to exon 53 skipping.[1,7,8] Dystrophin protein at Week 48 and 6-minute walk test (6MWT) results at Week 144 were the primary clinical endpoints. Among the patients who received Vyondys 53 in Part 2 of the study (n = 25) the normal dystrophin protein increased from baseline (0.10%) through Week 48 (1.02%; $P < 0.001$). In individual patient biopsies at Week 48, the dystrophin level ranged from 0.09% to 4.3%, with a mean per-patient 16.0-fold increase in dystrophin. At Week 48, the mean level of exon 53 skipping increased to 18.6% (SD, 13.2%; range, 2.6% to 150.3%) vs. 2.6% (SD, 4.1%; range, 0.0 to 14.7%) at baseline. The percent dystrophin-positive fibers scoring increased from 1.4% (SD, 2.4%; range, 0.06% to 9.8%) at baseline to 10.5% (SD, 10.1%; range, 0.9% to 32.6%) [$P < 0.001$) at Week 48. There was a mean per-patient 13.5-fold increase in percent dystrophin-positive fibers from baseline through Week 48. 6MWT results have not yet been reported.

8. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/13/2019
Annual Revision	No criteria changes.	12/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Natpara® (parathyroid hormone for subcutaneous injection – Shire-NPS Pharmaceuticals)

DATE REVIEWED: 04/22/2020

OVERVIEW

Natpara, a replica of the endogenous parathyroid hormone, is indicated as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism.[1] There are several limitations to Natpara use: because of the potential risk of osteosarcoma, Natpara is recommended only for patients who cannot be well-controlled on calcium supplements and active forms of vitamin D alone; it was not studied in patients with hypoparathyroidism caused by calcium-sensing receptor mutations; and it was not studied in patients with acute post-surgical hypoparathyroidism. The dose of Natpara should be individualized based on total serum calcium and 24-hour urinary calcium excretion. The initial dose of Natpara is 50 mcg once daily (QD) given as a subcutaneous injection; the dose may be decreased to as low as 25 mcg/day or increased to the maximum daily dose of 100 mcg.

Before initiating and during therapy with Natpara, 25-hydroxyvitamin D stores should be sufficient and serum calcium concentration should be > 7.5 mg/dL before initiating Natpara therapy.[1] In the pivotal study, a responder to Natpara therapy was defined as an individual who had: ≥ 50% reduction from baseline in the dose of active vitamin D, ≥ 50% reduction from baseline in the dose of oral calcium supplementation, and an albumin-corrected total serum calcium concentration between 7.5 mg/dL and 10.6 mg/dL.[1]

Natpara has a Boxed Warning about the risk of osteosarcoma.[1] Parathyroid hormone has been shown to increase the incidence of osteosarcoma in male and female rats; the risk was dependent on dose and treatment duration. A risk to humans could not be excluded. Natpara is available only through a restricted

Risk Evaluation and Mitigation Strategy (REMS) program; only certified healthcare providers can prescribe and only certified pharmacies can dispense Natpara.

Disease Overview

Hypoparathyroidism is a rare endocrine disorder that affects approximately 60,000 individuals in the US.[2,3] This condition is characterized by low calcium and high phosphate levels and low or inappropriately normal parathyroid hormone level.[4] The parathyroid hormone plays a critical role in maintaining calcium homeostasis and bone metabolism (osteoclasts and osteoblasts).[3,5-7] In some cases, the parathyroid glands produce insufficient parathyroid hormone and in other cases, the parathyroid glands have been removed.[2,5,8] The goals of treatment of hypoparathyroidism are to maintain serum calcium and the calcium-phosphate product within the normal range and avoid hypercalciuria.[4] The standard of care includes oral calcium and (active or parental) vitamin D to manage the hypocalcemia that results from the condition.[6-8] While these products maintain serum calcium concentration within normal limits and minimize the symptoms of hypocalcemia, they do not address the physiologic aspects of hypoparathyroidism. Additionally, there are long-term complications associated with calcium and vitamin D therapy, including renal function deterioration, renal stones, and soft tissue calcification.[3,6,9-11]

Guidelines/Recommendations

A consensus statement released in 2019 notes the use of calcium supplements and active vitamin D as the conventional therapy for hypoparathyroidism.[12] Although these therapies address the hypocalcemic aspect of hypoparathyroidism, they fail to provide a physiologic replacement of parathyroid hormone. Natpara therapy should be considered in patients experiencing inadequate control of serum calcium; patients who require > 2.5 g of calcium or > 1.5 µg of calcitriol per day to control serum calcium or symptoms; patients with hypercalciuria, renal stones, nephrocalcinosis, stone risk or reduced creatinine clearance or estimated glomerular filtration rate (eGFR) (< 60 mL/min); or patients with hyperphosphatemia and/or calcium-phosphate product > 55 mg^2/dL^2 or 4.4 $mmol^2/L^2$. Natpara therapy may also be beneficial in patients who have malabsorption or who are intolerant of large doses of oral calcium supplements or who are noncompliant with taking several tablets a day.

The First International Conference on the Management of Hypoparathyroidism provided some guidelines on the management of this condition (2016).[9] Conventional management of chronic hypoparathyroidism includes use of calcium supplements, active vitamin D or analogs, magnesium, thiazide diuretics (when necessary to help manage hypercalciuria and low salt diet), and phosphate binders and low phosphate diet (if necessary to control hyperphosphatemia). Natpara therapy may be considered in patients with well-established chronic hypoparathyroidism of any etiology except for autosomal dominant hypocalcemia; variable and inconsistent control of the serum calcium with frequent episodes of hypo- and hypercalcemia; nephrolithiasis, nephrocalcinosis, or reduced creatinine clearance or eGFR to < 60 mL/min; hypercalciuria and/or other biochemical indices or renal stone risk; persistently elevated serum phosphate and/or calcium-phosphate product (> 55 mg^2/dL^2 or 4.4 $mmol^2/L^2$); excessive amounts of oral medications required to control symptoms such as > 2.5 g of calcium or > 1.5 µg of active vitamin D, or both; and a gastrointestinal tract disorder that might lead to variable calcium and vitamin D absorption.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Natpara. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Natpara as well as the monitoring required for adverse events and long-term efficacy, approval requires Natpara to be prescribed by, or in consultation with, a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Natpara is recommended in those who meet the following criteria:

FDA-Approved Indications

31. Chronic Hypoparathyroidism. Approve for 3 years if the patient meets ONE of the following conditions (A or B):

A) Initial Therapy. Approve if the patient meets ALL of the following criteria (i, ii, iii, and iv)

- **i.** The patient cannot be well-controlled on calcium supplements and active forms of vitamin D alone; AND
- **ii.** The patient's 25-hydroxyvitamin D stores are sufficient (before initiating Natpara therapy) per the prescriber; AND
- **iii.** The patient's serum calcium concentration is > 7.5 mg/dL before initiating Natpara therapy; AND
- **iv.** The medication is prescribed by, or in consultation with, an endocrinologist.

B) Patient is Currently Receiving Natpara. Approve if the patient meets ALL of the following criteria (i, ii, and iii):

- **i.** The patient cannot be well-controlled on calcium supplements and active forms of vitamin D alone; AND
- **ii.** The patient's 25-hydroxyvitamin D stores are sufficient (during Natpara therapy) per the prescriber ; AND
- **iii.** The patient is responding to Natpara therapy (e.g., reduction in the patient's oral calcium dose; reduction in the patient's active vitamin D dose; maintenance of a stable albumin-corrected total serum calcium concentration), as determined by the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Natpara has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

181. Acute Post-Surgical Hypoparathyroidism. Natpara was only studied in patients with chronic hypoparathyroidism.

182. Hypoparathyroidism Caused by Calcium-Sensing Receptor Mutations. Natpara was not studied in this patient population.

183. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual revision	No criteria changes.	04/25/2018
Annual Revision	No criteria changes.	04/17/2019
Annual Revision	No criteria changes.	04/22/2020

PRIOR AUTHORIZATION POLICY

POLICY: Neurology – Brineura® (cerliponase alfa injection for intraventricular use – BioMarin)

DATE REVIEWED: 04/08/2020

OVERVIEW

Brineura is indicated to slow the loss of ambulation in symptomatic pediatric patients ≥ 3 years of age with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency.[1] Brineura is recombinant human TPP1 produced using recombinant DNA technology. The recommended dose of Brineura is 300 mg administered once every other week (QOW) via intracerebroventricular (ICV) infusion. Following Brineura administration, the patient must also receive an infusion of intraventricular electrolytes. The drug is administered into the cerebral spinal fluid via a surgically implanted reservoir and catheter. It should only be administered by or under the direction of a physician who is knowledgeable in ICV administration.

Disease Overview

CLN2 disease is an extremely rare neurodegenerative disorder that is part of a group neuronal ceroid lipofuscinoses (NCLs) sometimes referred to as Batten disease.[2] NCL diseases are a heterogenous group of incurable neurodegenerative lysosomal storage diseases. They manifest as early impairment of vision, loss of cognitive and motor functions, seizures, and premature death. To date, 13 genetic mutations have been discovered to cause the multiple variations of the disease (e.g., CLN1, CLN2, CLN3 etc.). Classic late infantile NCL disease is caused by a mutation in the CLN2 gene, which encodes for lysosomal TPP1. Without TPP1, lysosomal storage materials accumulate, contributing to the progressive and persistent neurogeneration.[2] In CLN2 disease, symptom onset is typically between 2 and 4 years of age, and lifespan is to around 6 to 14 years. Other NCLs result in deficiencies in enzymes other than TPP1. As Brineura is human recombinant TPP1, its efficacy is specific to CLN2 disease.

Clinical Efficacy

The efficacy of Brineura in CLN2 disease was assessed in patients 3 to 8 years of age and compared with a natural history cohort.[1] All patients had confirmed TPP1 deficiency. The Motor domain of the CLN2 Clinical Rating Scale assessed declining function, with scores ranging from 3 (indicating grossly normal) to 0 (profoundly impaired). Decline was defined as having an unreversed 2-category decline or an unreversed score of 0. At Week 96, the matched analysis demonstrated fewer patients declined in the Motor domain with Brineura-treated patients (n = 1/17) compared with untreated patients in the natural history cohort (n = 11/17).

Guidelines

Recently published expert recommendations state that patients with a suspected NCL disorder require NCL-specific diagnostic testing.[3] Patients require assessment by a metabolic specialist/geneticist, an NCL specialist, or a pediatric neurologist with experience in diagnosis NCL disorders. While there is no standardized method for identifying patients CLN2 disease, diagnosis is generally based on biochemical measurement of enzyme activity and genetic testing.[3-4]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Brineura. All approvals are provided for the duration noted below. Because of the of the specialized skills required for evaluation and diagnosis of patients treated with Brineura as well as the monitoring required for adverse events and long-term efficacy, approval requires Brineura to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Brineura is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Late Infantile Neuronal Ceroid Lipofuscinosis Type 2 (CLN2).** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   - **B)** The patient is ≥ 3 years of age; AND
   - **C)** The patient has a diagnosis of CLN2 disease as confirmed by ONE of the following (i or ii):
     - i. The patient has had a genetic test which confirms the diagnosis of CLN2 disease; OR
     - ii. The patient has had a test which confirms reduced activity of tripeptidyl peptidase 1 (TPP1); AND
   - **D)** Brineura is prescribed by or in consultation with a metabolic specialist, geneticist, pediatric neurologist, or a physician specializing in the treatment of neuronal ceroid lipofuscinoses (NCLs).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Brineura has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

1. **Neuronal Ceroid Lipofuscinoses (NCLs) other than late infantile ceroid lipofuscinosis type 2 (CLN2) [e.g., CLN1, CLN3, CLN10, CLN13, and others].** Brineura has not been studied for NCLs involving mutations in genes other than CLN2.[1]

2. Coverage is not recommended for circumstances *not* listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/10/2019
Annual revision	No changes to criteria.	04/08/2020

PRIOR AUTHORIZATION POLICY

POLICY: Neurology – Radicava® (edaravone intravenous injection – Mitsubishi Tanabe)

DATE REVIEWED: 04/08/2020

OVERVIEW

Radicava is indicated for the treatment of amyotrophic lateral sclerosis (ALS).[1] It is an anti-oxidative, free radical scavenger which eliminates lipid peroxide and hydroxyl radicals; however, it is unknown exactly how Radicava exerts its therapeutic effect in ALS.[1-2]

Disease Overview

ALS, also known as Lou Gehrig's disease, is a rapidly progressive, paralyzing disease characterized by degeneration of upper motor neurons (UMNs) and lower motor neurons (LMNs) in the brain, brainstem, and the spinal cord resulting in muscle weakness.[2-4] Patients with ALS typically present with painless, progressive muscle atrophy and weakness, which eventually leads to paralysis and death, primarily due to respiratory failure. The accurate diagnosis of ALS is challenging and delays in diagnosis are common (average diagnostic delay of 11 to 12 months or more). The El Escorial criteria (used in the clinical studies of Radicava) were developed to standardize the diagnosis of ALS (revised by Airlie House in 1999).[3-5] The average survival following diagnosis of ALS is approximately 3 years; 50% of patients will die within 30 months of symptom onset. However, median survival can range from months to several years and the rate of progression of the disease varies considerably between patients.

Clinical Efficacy

The efficacy of Radicava was established in one Phase III, randomized, double-blind, placebo-controlled, Japanese trial (published) [n = 137].[6] This study enrolled patients who had a "definite" or "probable" diagnosis of ALS (based on El Escorial and revised Airlie House criteria; criteria provided in the Appendix) and were living independently at the time of screening. Patients also were required to have functionally retained most activities of daily living (defined as a score of two points or better on each individual item of the ALS Functional Rating Scale – Revised [ALSFRS-R]), have normal respiratory function (i.e., a percent-predicted forced vital capacity [FVC] value ≥ 80%), and have a disease duration of ≤ 2 years. Overall, 91% of patients were also receiving riluzole. The decline in the ALSFRS-R scores from baseline to Week 24 was statistically significantly less with Radicava compared with placebo.[1,6] In a separate study involving patients with longer disease duration, reduced respiratory function, and less certain ALS diagnosis, Radicava did not demonstrate benefit vs. placebo.[7]

Guidelines

The American Academy of Neurology (AAN) practice parameter on the care of patients with ALS (last updated 2009; reaffirmed 2014) does not yet address Radicava.[8-9] The practice parameter states that riluzole is safe and effective for slowing disease progression to a modest degree and should be offered to patients with ALS. However, riluzole may result in fatigue in some patients and if the risk of fatigue outweighs modest survival benefits, discontinuation of riluzole may be considered. Referral to a specialized multidisciplinary clinic should be considered for patients with ALS to optimize health care delivery, prolong survival, and enhance quality of life. Additionally, noninvasive mechanical ventilation may lengthen survival and can be considered to improve quality of life and slow FVC decline. The European Federation of Neurological Societies (EFNS) guidelines on the clinical management of ALS (2012) also recommend patients be offered treatment with riluzole as early as possible after diagnosis.[10] However, patients with progressive muscular atrophy, primary lateral sclerosis, or hereditary spastic paraplegia should not be treated with riluzole.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Radicava. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the of the specialized skills required for evaluation and diagnosis of patients treated with Radicava as well as the monitoring required for adverse events and long-term efficacy, approval requires Radicava to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Radicava is recommended in those who meet the following criteria:

FDA-Approved Indications

2. Amyotrophic Lateral Sclerosis (ALS). Approve for 6 months if the patient meets ONE of the following (A or B):

E) Initial Therapy. Approve if the patient meets ALL of the following (i, ii, iii, iv, v, and vi):

i. According to the prescriber, the patient has a "definite" or "probable" diagnosis of amyotrophic lateral sclerosis (ALS) based on the application of the El Escorial or the revised Airlie House diagnostic criteria; AND

ii. Patient has a score of two points or more on each item of the ALS Functional Rating Scale – Revised (ALSFRS-R) [i.e., has retained most or all activities of daily living]; AND

iii. Patient has a percent-predicted forced vital capacity (FVC) ≥ 80% (i.e., has normal respiratory function); AND

iv. Patient has been diagnosed with ALS for ≤ 2 years; AND

v. Patient has received or is currently receiving riluzole tablets (Rilutek®, generics), Tiglutik® (riluzole oral suspension), or Exservan™ (riluzole oral film); AND

vi. Radicava is prescribed by or in consultation with a neurologist, a neuromuscular disease specialist, or a physician specializing in the treatment of ALS.

F) Patients Currently Receiving Radicava. Approve if the patient meets ALL of the following (i, ii, and iii):

i. Radicava is prescribed by or in consultation with a neurologist, a neuromuscular disease specialist, or a physician specializing in the treatment of ALS; AND

ii. According to the prescriber, the patient continues to benefit from therapy; AND

iii. The patient is not requiring invasive ventilation.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Radicava has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

184. **Aneurysmal Subarachnoid Hemorrhage.** Radicava is not indicated for the treatment of aneurysmal subarachnoid hemorrhage (SAH).[1] One randomized controlled study (published) [n = 91] evaluated the efficacy of Radicava (formulation/dose not specified) in patients with aneurysmal SAH.[11] At 3 months post-SAH, the incidence of delayed ischemic neurologic deficits (DINDs) in patients treated with Radicava was 10% vs. 21% in patients in a control group; the between-group treatment difference was not significant (P = 0.118). In patients who had DINDs, 66% of patients in the control group had a cerebral infarction caused by vasospasm compared with 0% of Radicava-treated patients (P = 0.028). Additional, well-designed clinical studies are needed to establish if Radicava has a role in therapy post-SAH.

185. **Myocardial Infarction.** Radicava is not indicated for the treatment of myocardial; there are no US or North American studies of Radicava for this indication.[1] One randomized, placebo-controlled, open-label, Japanese study (published) [n = 101] evaluated the effect of Radicava on the long term prognosis in patients experiencing an acute myocardial infarction.[12] Patients were randomized to receive either Radicava (foreign formulation) 30 mg intravenous (IV) or placebo immediately prior to reperfusion. In all patients, successful reperfusion was obtained within 6 hours post-symptom onset. Radicava significantly attenuated the infarct size and incidence of reperfusion arrhythmia compared with placebo (P = 0.035 and P = 0.031, respectively). Further research is warranted to determine if Radicava has a place in therapy in the management of AMI.

186. **Radiation-Induced Brain Injury.** Radicava is not indicated for the treatment of radiation-induced brain injury; there are no US or North American studies of Radicava for this indication.[1] One randomized, open-label, 3-month, Chinese study (published) [n = 137] evaluated the protective effect of Radicava on radiation-induced brain necrosis in patients with nasopharyngeal carcinoma.[13] Patients were randomized to receive Radicava (foreign formulation) 30 mg intravenous (IV) twice daily for 2 weeks (not FDA-approved dosing) + IV corticosteroid therapy or placebo + IV corticosteroid therapy. Following 3 months of therapy, radiologic improvement (reduction in edema of ≥ 25%) was observed in 55.6% of patients who received Radicava (n = 40/72) compared with 35.4% of patients treated with placebo (n = 23/65) [P = 0.025]. The area of T1-weighted contrast enhancement was reduced from baseline with both Radicava and placebo (-1.67 cm and -1.20 cm, respectively); however, the difference between the treatment arms was not statistically significant. Improvement in neurologic signs and symptoms evaluated by the Late Effects of Normal Tissues – Subjective, Objective, Management, Analytic (LENT/SOMA) scale was also observed in 61.1% of Radicava-treated patients vs. 38.5% of placebo-treated patients (P = 0.006). Further research is warranted to determine if Radicava has a place in therapy in the treatment of radiation-induced brain injury.

187. **Retinal Vein Occlusion.** Radicava is not indicated for the prevention of macular edema and improvement of visual acuity after arteriovenous sheathotomy in patients with branch retinal vein occlusion; there are no US or North American studies of Radicava for this indication.[1] A single, small, prospective, Japanese study [published] (n = 47) evaluated the efficacy of Radicava (foreign formulation) in patients with branch retinal vein occlusion undergoing vitrectomy.[14] Patients either received Radicava 30 mg IV at the time of the procedure or no additional therapy. Visual acuity was measured before and 12 months after the procedure. At 12 months following the operation, the logarithm of the minimum angle of resolution (logMAR) units improved from 0.22 to 0.56 logMAR units in patients who had received Radicava and from 0.20 to 0.27 logMAR units in patients who did not receive active treatment (P = 0.016). Additional data are needed to support the use of Radicava for this indication.

188. **Sensorineural Hearing Loss.** Radicava is not indicated for the treatment of sensorineural hearing loss; there are no US-based studies of Radicava for this indication.[1] One small, Japanese study evaluated 14 patients with idiopathic sudden sensorineural hearing loss were treated with Radicava (foreign formulation; dose not specified).[15] These patients were compared with a control group of 14 patients with similar prognostic factors who had been treated with hyperbaric oxygenation therapy. No significant differences were observed between the Radicava group and the control group.

189. Stroke. Radicava is not FDA-approved for the treatment of patients who have experienced stroke.[1] Radicava has been approved in other countries for this indication and there are some foreign data supporting its use.[16] There are no US-based studies of Radicava for stroke at this time. A systematic review assessed available efficacy data from three clinical trials (n = 496) of Radicava for acute ischemic stroke.[17] These trials compared Radicava 30 mg twice daily IV infusion for 14 days + another treatment vs. the other treatment alone within 72 hours of stroke symptom onset. One trial did not find significantly reduced mortality with Radicava vs. the control group; the other two studies did not report this endpoint. Overall, there was a significantly higher proportion of patients who had neurologic improvement in the Radicava group vs. control.

190. Coverage is not recommended for circumstances *not* listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/10/2019
Annual revision	**Amyotrophic Lateral Sclerosis:** For the criteria applying to initial therapy diagnosis of amyotrophic lateral sclerosis and for patients currently receiving Radicava who have responded, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). Exservan (riluzole oral film) was added as an option for criterion requiring the patient has received or is currently receiving	04/08/2020

	riluzole tablets (Rilutek, generics) or Tiglutik (riluzole oral suspension).	

APPENDIX*

El Escorial criteria for the diagnosis of ALS were initially developed by the World Federation of Neurology (WFN) in 1990. In 1998, the WFN held a workshop for the Research Committee on Motor Neuron Diseases at the Airlie Conference Center in Virginia, which resulted in a revision of the guidelines in 2000. The pivotal study of Radicava references the El Escorial criteria updated by the WFN in 2000 (Airlie House). According to these guidelines, the diagnosis of ALS requires:

The presence of:

- Evidence of lower motor neuron (LMN) degeneration by clinical, electrophysiological or neuropathologic examination; AND
- Evidence of upper motor neuron (UMN) degeneration by clinical examination; AND
- Progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination.

Together with the absence of:

1. Electrophysiological or pathological evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration; AND
2. Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs.

Without pathological confirmation, the diagnosis of ALS may be categorized into levels of certainty using clinical assessment. The following terms are used to describe the categories of diagnostic certainty.

- **Clinically Definite ALS:** defined on clinical evidence alone by the presence of UMN, as well as LMN signs, in the bulbar region and at least two spinal regions or the presence of UMN and LMN signs in three spinal regions.
- **Clinically Probable ALS:** defined on clinical evidence alone by UMN and LMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs.
- **Clinically Probable ALS – Laboratory-supported:** defined when clinical signs of UMN and LMN dysfunction are in only one region, or when UMN signs alone are present in one region, and LMN signs defined by EMG criteria are present in at least two regions, with proper application of neuroimaging and clinical laboratory protocols to exclude other causes.
- **Clinically Possible ALS:** defined when clinical signs of UMN and LMN dysfunction are found together in only one region or UMN signs are found alone in two or more regions; or LMN signs are found rostral to UMN signs and the diagnosis of Clinically Probable ALS – Laboratory supported cannot be proven by evidence on clinical grounds in conjunction with electrodiagnostic, neurophysiologic, neuroimaging or clinical laboratory studies. Other diagnoses must have been excluded to accept a diagnosis of Clinically Possible ALS.

*** This appendix is for reference; it is NOT intended that patients meet the above criteria for approval of Radicava.**

PRIOR AUTHORIZATION POLICY

POLICY: Neurology – Riluzole Products Prior Authorization Policy

- Exservan™ (riluzole oral film – Covis Pharmaceuticals/Aquestive)
- Rilutek® (riluzole tablets – Covis Pharma; generics)
- Tiglutik® (riluzole oral suspension – ITF Pharma)

REVIEW DATE: 07/22/2020

OVERVIEW

All of the available riluzole products are indicated for the treatment of amyotrophic lateral sclerosis (ALS).[1,2,9] Riluzole is a member of the benzothiazole class; the mechanism by which it exerts its effects in patients with ALS is unknown. Riluzole tablets were initially approved by the FDA in 1995.[1] In the years since, two additional riluzole formulations, Exservan oral film and Tiglutik oral suspension, have been approved.[2,9]

Disease Overview

ALS, also known as Lou Gehrig's disease, is a rapidly progressive, paralyzing disease characterized by degeneration of upper motor neurons (UMNs) and lower motor neurons (LMNs) in the brain, brainstem, and the spinal cord resulting in muscle weakness.[3-5] Patients with ALS typically present with painless, progressive muscle atrophy and weakness, which eventually leads to paralysis and death, primarily due to respiratory failure. The accurate diagnosis of ALS is challenging and delays in diagnosis are common (average diagnostic delay of 11 to 12 months or more). The average survival following diagnosis of ALS is approximately 3 years; 50% of patients will die within 30 months of symptom onset. However, median survival can range from months to several years and the rate of progression of the disease varies considerably between patients.

Guidelines

The American Academy of Neurology (AAN) practice parameter on the care of patients with ALS (last updated 2009; reaffirmed 2020) states that riluzole should be offered to patients with ALS (Level A recommendation), as it is safe and effective for modestly slowing disease progression.[6,7] Based on available clinical trial data, the AAN estimates riluzole prolongs survival by 2 to 3 months. However, some large cohort studies that estimate survival to be prolonged for up to 21 months. Of note, a previous practice advisory from the AAN (1997) had recommended riluzole only in patients with definite or probable ALS of < 5 years duration, with a forced vital capacity (FVC) > 60% and without tracheostomy. However, the 2012 parameter does not include any stipulations on which patients should use riluzole. Riluzole may result in fatigue in some patients and if the risk of fatigue outweighs modest survival benefits, discontinuation of riluzole may be considered (Level C recommendation). The European Federation of Neurological Societies (EFNS) guidelines on the clinical management of ALS (2012) also recommend patients be offered treatment with riluzole as early as possible after diagnosis.[8] While it is noted that riluzole may be less effective in patients with late-stage disease, it is unclear when or if treatment should be discontinued. Patients with progressive muscular atrophy, primary lateral sclerosis, or hereditary spastic paraplegia are not recommended to use riluzole as they were not included in the clinical studies. However, some of these patients fall within the ALS syndrome and therefore may benefit from treatment with riluzole.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of riluzole. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with riluzole as well as the monitoring required for adverse events and long-term efficacy, approval requires riluzole to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of riluzole is recommended in those who meet the following criteria:

FDA-Approved Indications

131. Amyotrophic Lateral Sclerosis (ALS). Approve for 1 year if the agent is prescribed by or in consultation with a neurologist, a neuromuscular disease specialist, or a physician specializing in the treatment of ALS.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of riluzole is not recommended in the following situations:

145. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/24/2019
Selected Revision	Added Exservan to the policy.	12/18/2019
Annual revision	No change to criteria.	07/22/2020

PRIOR AUTHORIZATION POLICY

POLICY: Northera Prior Authorization Policy

- Northera® (droxidopa capsules – Chelsea Therapeutics)

REVIEW DATE: 12/02/2020

OVERVIEW

Northera, a norepinephrine-type product, is indicated for the treatment of orthostatic dizziness, lightheadedness or the "feeling that one is about to black out" in adult patients with **symptomatic neurogenic orthostatic hypotension (NOH)** caused by primary autonomic failure (Parkinson's disease [PD], multiple system atrophy [MSA], and pure autonomic failure [PAF]), dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy.[1] According to the prescribing information, the effectiveness beyond 2 weeks of treatment has not been established and should be evaluated periodically.

Disease Overview

Orthostatic hypotension (OH) is a sustained reduction in systolic blood pressure (SBP) of at least 20 mmHg or diastolic blood pressure (DBP) of 10 mmHg within 3 minutes of standing or head-up tilt to at least 60° on a tilt table.[2] OH may be symptomatic or asymptomatic, with only symptomatic OH requiring treatment.[3] NOH is a specific subset of this condition, in which OH is due to inadequate release of norepinephrine from sympathetic vasomotor neurons leading to vasoconstrictor failure.[2] NOH is a rare, chronic and often debilitating condition that is associated with PD (prevalence: 16% to 58%), MSA (prevalence: 60% to 75%), and PAF (prevalence: 100%) and with peripheral neuropathies and ganglionopathies that affect the autonomic nerves.[2,3] Symptoms of NOH include dizziness, lightheadedness, blurred vision, fatigue, and fainting upon standing up.[2] These symptoms can adversely affect patients' quality of life and ability to conduct activities of daily living that involve standing or walking. Many patients with NOH have supine hypertension (i.e., high BP when lying down) even before treatment of hypotension is initiated. Medications may increase the frequency of symptomatic NOH, such as alpha-adrenergic antagonists (e.g., benign prostatic hypertrophy medications), antidepressants (particularly, tricyclic antidepressants), antipsychotics, and dopaminergic agonists (e.g., antiparkinsonian medications).[3]

Treatment of symptomatic NOH is aimed at increasing standing SBP into the range of compensatory cerebrovascular autoregulation (approximately 50 to 150 mmHg).[4,5] Unapproved pharmacologic agents include fludrocortisone (volume expansion and pressor effect), desmopressin (nasal spray or oral) [volume expansion], dihydroergotamine (oral) [pressor effect], indomethacin (oral or intravenous) [pressor effect], pyridostigmine, and erythropoietin (treatment of anemia of chronic autonomic failure can improve orthostatic intolerance).[6-8] Midodrine, an $alpha_1$-agonist, is the only other medication approved with a similar indication (treatment of symptomatic OH) to Northera.[9]

Clinical Efficacy

Northera was evaluated in one 12-month, open-label study which demonstrated the maintenance of improvements from baseline in patient-reported NOH symptom severity and impact on daily activities.[6] Small studies have been published for the use of Northera in hemodialysis patients to prevent orthostatic hypotension (OH)[10,11] and also in restoring neurologic deficit in chronic stoke patients.[12]

Safety
Northera has a Boxed Warning regarding supine hypertension. Northera may cause or exacerbate supine hypertension in patients with NOH. Supine BP should be measured prior to initiating Northera and after dose increases.

Guidelines
According to the American Academy of Neurology (AAN) practice parameter on treatment of nonmotor symptoms of PD (2010), there have been few placebo controlled trials of treatment for OH in PD, and the available data are insufficient to make a recommendation on the use of specific treatments for OH in PD.[13] Small studies have used domperidone, fludrocortisone, and indomethacin. While studies are lacking for mineralocorticoids, alpha-sympathomimetics, and pyridostigmine, they have pharmacologic actions that are consistent with improvement in OH. The only medications currently approved to treat OH are midodrine and Northera.

Consensus panel recommendations initiated by the American Autonomic Society and the National Parkinson Foundation for the screening, diagnosis, and treatment of NOH and associated supine hypertension were published in 2017.[14] Once a patient is diagnosed with NOH, the goals of treatment should be to reduce the burden of symptoms (especially falls), prolong standing time, and restore independence in activities of daily living. The recommendations propose a four-step treatment algorithm for NOH: assessing and adjusting pre-existing medications that may be causing or exacerbating NOH, utilizing non-pharmacologic approaches (e.g., blood volume repletion, increased salt intake, physical conditioning, compression garments, elevating the head of the bed), implementing single-agent pharmacologic treatment, and with great caution, combining pharmacologic treatments. After each step, a 2-week assessment period is recommended to establish whether sufficient symptomatic benefit has been achieved before moving onto the next step. Recommended treatments include midodrine, Northera, fludrocortisone, and pyridostigmine. The initial choice of NOH treatments should be individualized and should consider severity, comorbid disease (especially cardiac or renal failure), and treatment goals. Based on the experience of the consensus panel, the recommendation is to titrate to maximum tolerable dose of a single medication and then, if symptomatic benefit is not obtained, consider switching to a different medication or adding a second agent and titrate from its lowest starting dose.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Northera. Because of the specialized skills required for evaluation and diagnosis of patients treated with Northera as well as the monitoring required for adverse events and long-term efficacy, approval requires Northera to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Northera is recommended in those who meet the following criteria:

FDA-Approved Indications

81. Neurogenic Orthostatic Hypotension (NOH). Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND

B) Patient has been diagnosed with symptomatic NOH due to primary autonomic failure (Parkinson's disease [PD], multiple system atrophy [MSA], and pure autonomic failure [PAF]), dopamine beta-hydroxylase deficiency, or non-diabetic autonomic neuropathy; AND

C) The medication has been prescribed by or in consultation with a cardiologist or a neurologist; AND

D) Patient has tried two other medications; AND
Note: Examples of other medications include fludrocortisone, desmopressin, dihydroergotamine, indomethacin, pyridostigmine, erythropoietin, midodrine.

E) Patient has initiated non-pharmacological measures including but not limited to elevation of the head of the bed, orthostatic compression garments, and appropriate physical training.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Northera is not recommended in the following situations:

191. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No change to criteria.	11/21/2018
Annual Revision	No change to criteria.	11/20/2019
Annual Revision	No change to criteria.	12/02/2020

PRIOR AUTHORIZATION POLICY

POLICY: Nuedexta Prior Authorization Policy

- Nuedexta® (dextromethorphan hydrobromide and quinidine sulfate capsules – Avanir)

REVIEW DATE: 08/19/2020

OVERVIEW

Nuedexta, a combination product containing dextromethorphan hydrobromide (DM) and quinidine sulfate, is indicated for the treatment of pseudobulbar affect.[1]

DM is a sigma-1 receptor agonist and an uncompetitive *N*-methyl-D-aspartate receptor antagonist.[1] Quinidine increases plasma levels of DM by competitively inhibiting cytochrome P450 2D6, which catalyzes a major biotransformation pathway for DM. The mechanism by which DM exerts therapeutic effects in patients with pseudobulbar affect is unknown. The recommended starting dose is one capsule daily (20 mg of DM and 10 mg of quinidine) by mouth for the initial 7 days of therapy. Thereafter, the daily dose should be two capsules/day (40 mg of DM and 20 mg of quinidine), given as one capsule every 12 hours (BID). The need for continued treatment should be reassessed periodically, as spontaneous improvement of pseudobulbar affect occurs in some patients.

Disease Overview

Pseudobulbar affect is a neurologic condition characterized by involuntary outbursts of laughing and/or crying incongruous or disproportionate to the patients' emotional state.[2,7] There are many terms that have been used to describe this condition, including pathological laughing and crying, affective lability, emotional incontinence, emotionalism, and involuntary emotional expression disorder.[7] Pseudobulbar affect, hypothesized to arise from disconnection of brainstem structures from cortical inhibition, is associated with underlying central nervous system disorders including stroke, traumatic brain injury, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS).[2] It is estimated that pseudobulbar affect impacts more than 1 million people in the US diagnosed with neurological disease or brain injury.[7] Prevalence studies have reported that pseudobulbar affect affects 11% of patients one year after a stroke, 11% of patients during the first year after traumatic brain injury, 18% of patients with Alzheimer's disease, 10% of patients with MS, and 49% of patients with ALS.[2] In addition to the effects of the underlying disorder, pseudobulbar affect pseudobulbar affect can have a severe impact on well-being and social functioning and can be highly disabling, owing in part to the stigma attached to loss of emotional control. Episodes of laughing can also lead to respiratory compromise, especially in patients with a neurological disorder that already compromises respiratory function, such as ALS.[7] For these reasons, treatment should be strongly considered in any patient with pseudobulbar affect. The goal of therapy is to reduce the frequency of attacks.

Clinical Efficacy

The efficacy of Nuedexta was established in one trial in patients with pseudobulbar affect with underlying ALS or MS.[1,2] Two additional trials conducted with higher doses (DM 30 mg/quinidine 30 mg) provided supportive evidence.[3,4] PRISM II, an open-label, 90-day, published study, evaluated Nuedexta in patients with pseudobulbar affect and a diagnosis of dementia, stroke, or traumatic brain injury (n = 367).[8] Nuedexta was shown to be an effective treatment for pseudobulbar affect secondary to dementia, stroke, or traumatic brain injury, showing similar improvement to that reported in patients with pseudobulbar affect secondary to ALS or MS.

Guidelines

There are no guidelines specific to the management of pseudobulbar affect. However, the American Academy of Neurology (AAN) published an evidence-based guideline on the assessment and management of psychiatric disorders in individuals with MS.[5] The guideline found that Nuedexta is possibly effective

and may be considered for treating individuals with MS with pseudobulbar affect (Level C, one Class II study). Also, prior to the approval of Nuedexta, the AAN published a practice parameter on the care of the patient with ALS.[6] With regard to pharmacologic measures to reduce pseudobulbar affect, the AAN concludes that the combination DM/quinidine product is probably effective for pseudobulbar affect in ALS based on one Class I study[3], although side effects may limit its usefulness. Therefore, the AAN recommends that if approved by the FDA, and if side effects are acceptable, the combination DM/quinidine product should be considered for symptoms of pseudobulbar affect in patients with ALS (Level B). No other pharmacologic agents are addressed in the practice parameter for use in the management of pseudobulbar affect.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Nuedexta. Because of the specialized skills required for evaluation and diagnosis of patients treated with Nuedexta as well as the monitoring required for adverse events and long-term efficacy, approval requires Nuedexta to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nuedexta is recommended in those who meet the following criteria:

FDA-Approved Indications

3. **Treatment of Pseudobulbar Affect.** Approve for 1 year if the patient meets BOTH of the following criteria (A and B):
   - **A)** Patient has pseudobulbar affect associated with a chronic neurological condition; AND
     Note: Examples of chronic neurological conditions include amyotrophic lateral sclerosis, multiple sclerosis, stroke, dementia, traumatic brain injury.
   - **B)** Nuedexta is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nuedexta is not recommended in the following situations:

1. **Heroin Detoxification.** Limited published data are available in patients undergoing heroin detoxification.[9] The available study was conducted with the DM 30 mg/quinidine 30 mg formulation, using daily doses of DM 60 mg/quinidine 60 mg (dose cannot be achieved with Nuedexta capsules). There were no differences between DM/quinidine and placebo with regard to reducing opioid withdrawal symptoms.

2. **Levodopa-Induced Dyskinesia in Parkinson's Disease.** A single pilot study demonstrated benefit with dextromethorphan/quinidine for treating levodopa-induced dyskinesia in Parkinson's disease.[12] Larger studies with a longer treatment duration are needed to define the place in therapy for Nuedexta in this condition.

3. **Neuropathic Pain.** Limited published data are available in patients (n = 36) with diabetic peripheral neuropathic (DPN) pain (open-label tolerability study).[10] The available study was conducted with the DM 30 mg/quinidine 30 mg formulation, using daily doses up to DM 120 mg/quinidine 120 mg (dose

cannot be achieved with Nuedexta capsules). Higher daily doses of DM and quinidine (60 mg/60 mg and 90 mg/60 mg [doses cannot be achieved with Nuedexta capsules]) have also been evaluated in patients with DPN pain (n = 379) in one Phase III, randomized, placebo-controlled 13-week study.[7] Both DM/quinidine treatment groups had significant reductions in mean daily pain scores vs. placebo. More data are needed to define the place in therapy of Nuedexta in the treatment of neuropathic pain.

4. **Psychosis-Related Aggression**. A case series (n = 4) supports DM/quinidine as a potential alternative to conventional regimens for treating aggression and impulsive behavior in patients with psychotic disorder.[11] More data are needed to define the place in therapy of Nuedexta in the treatment of psychosis-related aggression.

5. **Treatment-Resistant Depression.** A Phase II, open-label, proof-of-concept study (n = 20) demonstrated preliminary efficacy for DM 45 mg/quinidine 10 mg every 12 hours. This dosing could not be achieved with Nuedexta capsules.[13] Additional data are needed to define the place in therapy for Nuedexta in the treatment of treatment-resistant depression.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Levodopa-induced dyskinesia in Parkinson's disease, psychosis-related aggression, and treatment-resistant depression were added to the Conditions Not Recommended for Approval due to very limited data.	08/01/2018
Annual Revision	No change to criteria.	08/07/2019

Annual Revision	No change to criteria. For the coverage condition of Treatment of Pseudobulbar Affect, examples of chronic neurological conditions were moved to a note.	08/19/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Abiraterone Acetate (Zytiga) Prior Authorization Policy
- Abiraterone Acetate (Zytiga® tablets – Janssen Biotech Inc., generics)

REVIEW DATE: 01/06/2021

OVERVIEW

Abiraterone acetate, an androgen biosynthesis inhibitor, is indicated for following uses **in combination with prednisone**:[1]
- **Metastatic castration-resistant prostate cancer** (mCRPC).
- **Metastatic high-risk castration-sensitive prostate cancer** (mCSPC).

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on prostate cancer (version 3.2020 – November 17, 2020) have the following recommendations for drug therapies (primarily focusing on oral agents, abiraterone acetate and Xtandi® [enzalutamide capsules]):[2]

- At initial diagnosis, for patients classified in the regional risk group (metastases in regional nodes [N1] with no distant metastases [M0]) and with a > 5 year expected patient survival or symptomatic, external beam radiation therapy (EBRT) + androgen deprivation therapy (ADT) [preferred] ± abiraterone acetate and prednisone is a recommended option (category 2A). ADT (without EBRT) ± abiraterone and prednisone is also a category 2A recommended option in this setting.
- If patients are positive for distant metastasis (M1) and have castration-naïve disease, ADT + abiraterone and prednisone and ADT + docetaxel are both category 1 recommended options. Other options are also available.
- For patients who progress to CRPC and are positive for distant metastasis, M1 and there are no visceral metastases, abiraterone and prednisone, docetaxel, Xtandi, sipuleucel-T, and Xofigo® (radium Ra 223 dichloride injection, for intravenous use) [for symptomatic bone metastases] are all category 1 preferred regimens.
  - If there are visceral metastases, Xtandi and docetaxel are category 1 recommended options. Abiraterone and prednisone, mitoxantrone with prednisone, or other secondary hormone therapies are other options (all category 2A).
  - For no visceral metastases, if patients had received prior therapy with Xtandi or abiraterone, then docetaxel and Xofigo are the category 1 options for subsequent therapy. If patients received prior docetaxel therapy, then Xtandi, abiraterone, Xofigo, and cabazitaxel are the category 1 options. For subsequent therapy with visceral metastases, docetaxel is the recommended category 1 option, if either Xtandi or abiraterone were used as prior therapies. For prior therapy with docetaxel, Xtandi, abiraterone, cabazitaxel are the recommended category 1 options.

The STAMPEDE trial assessed the efficacy of abiratereone acetate and prednisone in combination with ADT in newly diagnosed patients with metastatic, node-positive, or high-risk locally advanced prostate cancer.[4] About 20% of the patients had node-positive non-metastatic disease. However, the guidelines note that there was insufficient data available for failure-free survival and follow-up to recommend abiraterone for men with high-risk or very high-risk N0 M0 prostate cancer and more data are needed.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of abiraterone acetate. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of abiraterone acetate is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Prostate Cancer – Metastatic, Castration-Resistant (mCRPC).** Approve for 3 years if the patient meets the following conditions (A and B):
   - **A)** The medication is used in combination with prednisone; AND
   - **B)** Patient meets ONE of the following criteria (i or ii):
     - **i.** The medication is concurrently used with a gonadotropin-releasing hormone (GnRH) analog.
       Note: Examples are Lupron (leuprolide for injection), Lupron Depot (leuprolide acetate for depot suspension), Trelstar (triptorelin pamoate for injectable suspension), Zoladex (goserelin acetate implant), Vantas (histrelin acetate subcutaneous implant), Firmagon (degarelix for injection), Orgovyx (relugolix tablets); OR
     - **ii.** Patient has had a bilateral orchiectomy.

2. **Prostate Cancer –Metastatic, Castration-Sensitive (mCSPC).** Approve for 3 years if the patient meets the following criteria (A, B, and C):
   - **A)** The medication is used in combination with prednisone; AND
   - **B)** Patient has high-risk disease (e.g., evidence of measurable visceral metastases, lesions on bone scan, total Gleason score ≥ 8) as confirmed by the prescribing physician; AND
   - **C)** Patient meets ONE of the following criteria (i or ii):
     - **i.** The medication is concurrently used with a gonadotropin-releasing hormone (GnRH) analog.
       Note: Examples are Lupron (leuprolide for injection), Lupron Depot (leuprolide acetate for depot suspension), Trelstar (triptorelin pamoate for injectable suspension), Zoladex (goserelin acetate implant), Vantas (histrelin acetate subcutaneous implant), Firmagon (degarelix for injection), Orgovyx (relugolix tablets); OR
     - **ii.** Patient has had a bilateral orchiectomy.

Other Uses with Supportive Evidence

3. **Prostate Cancer – Regional Risk Group.** Approve for 3 years if the patient meets all of the following criteria (A, B, and C):
   - **A)** The medication is used in combination with prednisone; AND
   - **B)** Patient has regional lymph node metastases and no distant metastases; AND
   - **C)** Patient meets one of the following criteria (i or ii):
     - **i.** The medication with prednisone is used in combination with gonadotropin-releasing hormone (GnRH) analog.
       Note: Lupron (leuprolide acetate for injection), Lupron Depot (leuprolide acetate for depot suspension), Trelstar (triptorelin pamoate for injectable suspension), Zoladex (goserelin acetate implant), Vantas (histrelin acetate subcutaneous implant), Firmagon (degarelix for injection), Orgovyx (relugolix tablets); OR
     - **ii**. Patient has had an orchiectomy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of abiraterone acetate is not recommended in the following situations:

192. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Zytiga™ tablets [prescribing information]. Horsham, PA: Centocor Ortho Biotech, Inc; October 2020.
2. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (version 3. 2020 – November 17, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed January 3, 2021.
3. The NCCN Drugs and Biologics Compendium. © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed January 3, 2021. Search term: abiraterone acetate.
4. James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med.* 2017;377:338-351.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	Changed name of policy due to the addition of generics to Zytiga. Where appropriate, throughout the policy changed Zytiga to abiraterone acetate or "the medication".	02/06/2019
Annual Revision	Deleted "Locally Advanced" from indication descriptor for "Prostate Cancer – Regional Risk Group, Locally Advanced". Deleted "Prostate Cancer – Metastatic (Castration-Resistant or Castration-Sensitive) Post-External Beam Radiation Therapy" since these patients would be covered under conditions #1 or #2. Added criteria for concomitant use of abiraterone with gonadotropin releasing hormone agonist or patient has had a bilateral orchiectomy, as per prescribing information dosing requirements.	02/19/2020
Selected Revision	Changed gonadotropin-releasing hormone "agonist" to "analog" for all conditions. Added Firmagon as an example.	03/04/2020
Early Annual Revision	**Prostate Cancer Indications:** Added Orgovyx as an example of gonadotropin-releasing hormone analog.	01/06/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Afinitor Prior Authorization Policy

- Afinitor® (everolimus tablets – Novartis, generics 2.5 mg, 5 mg, 7.5 mg)
- Afinitor Disperz® (everolimus tablets for oral suspension – Novartis)

REVIEW DATE: 01/27/2021

OVERVIEW

Afinitor, a kinase inhibitor, is indicated for the following conditions:[1]

- **Breast cancer**, treatment of postmenopausal women with advanced hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative disease (advanced HR+ breast cancer) in combination with exemestane, after failure of treatment with letrozole or anastrozole.
- **Neuroendocrine tumors (NET)**, treatment of adult patients with progressive disease of pancreatic origin (PNET) and adults with progressive, well-differentiated, non-functional NET of gastrointestinal or lung origin that are unresectable, locally advanced or metastatic. Limitation of Use: Afinitor is not indicated for the treatment of patients with functional carcinoid tumors.
- **Renal cell carcinoma**, treatment of adult patients with advanced disease after failure of treatment with Sutent® (sunitinib capsules) or Nexavar® (sorafenib tablets).

- **Tuberous sclerosis complex (TSC)-associated renal angiomyolipoma,** treatment of adult patients with this disease not requiring immediate surgery.
- **TSC-associated subependymal giant cell astrocytoma (SEGA)**, treatment of adult and pediatric patients ≥ 1 year of age with TSC for the treatment of SEGA that requires therapeutic intervention but cannot be curatively resected. Afinitor Disperz is also FDA-approved for this indication.
- **TSC-associated partial-onset seizures**, adjunctive treatment of adult and pediatric patients ≥ 2 years of age. Afinitor Disperz is FDA-approved for this indication.

Of note, Zortress®, (everolimus tablets) is indicated in combination with other drugs for prophylaxis of organ rejection in adult patients undergoing kidney or liver transplant.[2] The tablet strengths and dosing is different for Zortress than with Afinitor.

Guidelines

The National Comprehensive Cancer Network (NCCN) Compendium recommends use of everolimus for the indications listed in the FDA-approved and Other Uses with Supportive Evidence sections.[3] All of the recommendations are category 1 or category 2A.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Afinitor and Afinitor Disperz. All approvals are provided for the duration noted below. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: a woman is defined as an individual with the biological traits of a woman, regardless of the individual's gender identity or gender expression; men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Afinitor (generics) and Afinitor Disperz is recommended in those who meet the following criteria:

FDA-Approved Indications

32. Breast Cancer. Approve for 3 years if the patient meets the following criteria (A, B, C, D, E, and F):
- **A)** Patient has recurrent or Stage IV, hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND
- **B)** Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
- **C)** Patient has tried at least one prior endocrine therapy (e.g., anastrozole, letrozole, or tamoxifen); AND
- **D)** Patient meets ONE of the following conditions (i or ii):
  - **i.** Patient is a postmenopausal female* or a male*; OR
  - **ii.** Patient is premenopausal or perimenopausal AND is receiving ovarian suppression/ablation with a gonadotropin-releasing hormone (GnRH) agonist or has had surgical bilateral oophorectomy or ovarian irradiation; AND
    Note: Examples are Lupron® (leuprolide), Trelstar® (triptorelin), Zoladex® (goserelin).
- **E)** Patient meets ONE of the following conditions (i or ii):
  - **i.** If patient is a male AND if Afinitor will be used in combination with exemestane, the patient is receiving a gonadotropin-releasing hormone (GnRH) agonist; OR
    Note: Examples are Lupron [leuprolide], Trelstar [triptorelin], Zoladex (goserelin).
  - **ii.** Afinitor will be used in combination with exemestane, fulvestrant, or tamoxifen; AND
- **F)** Patient has not had disease progression while on Afinitor.

***** Refer to the Policy Statement.

33. **Neuroendocrine Tumors of the Pancreas, Gastrointestinal Tract, Lung and Thymus (Carcinoid Tumors) – Advanced, Unresectable, or Metastatic.** Approve for 3 years.

34. **Renal Cell Carcinoma (Clear Cell or Non-Clear Cell Histology).** Approve for 3 years if the patient meets the following criteria (A and B):
    A) Patient has relapsed or Stage IV disease; AND
    B) If using for clear cell disease, the patient has tried at least one prior systemic therapy.
    Note: Examples of prior systemic therapy are Inlyta [axitinib tablets], Votrient (pazopanib tablets), Sutent (sunitinib capsules), Cabometyx (cabozantinib tablets), Nexavar [sorafenib tablets].

4. **Tuberous Sclerosis Complex (TSC)-Associated Renal Angiomyolipoma.** Approve for 3 years.

5. **Tuberous Sclerosis Complex (TSC)-Associated Subependymal Giant Cell Astrocytoma (SEGA).** Approve for 3 years if therapeutic intervention is required but SEGA cannot be curatively resected.

6. **Tuberous Sclerosis Complex (TSC)-Associated Partial Onset Seizures.** Approve for 3 years.

Other Uses with Supportive Evidence

7. **Differentiated (i.e., papillary, follicular, and Hürthle cell) Thyroid Carcinoma.** Approve for 3 years if refractory to radioactive iodine therapy.

8. **Endometrial Carcinoma.** Approve for 3 years if the patient meets the following criteria (A and B):
    A) The medication will be used in combination with letrozole; AND
    B) Patient has recurrent, metastatic, or high-risk disease.

9. **Gastrointestinal Stromal Tumors (GIST).** Approve for 3 years if the patient meets the following criteria (A, B, C, and D):
    A) Patient has tried imatinib (Gleevec® tablets, generics); AND
    B) Patient has tried Sutent® (sunitinib capsules); AND
    C) Patient has tried Stivarga® (regorafenib tablets); AND
    D) The medication will be used in combination with imatinib (Gleevec tablets, generics), Sutent, or Stivarga.

10. **Classic Hodgkin Lymphoma.** Approve for 3 years in adults ≥ 18 years of age with relapsed or refractory disease.

11. **Meningioma.** Approve for 3 years if the patient has recurrent or progressive disease.

12. **Soft Tissue Sarcoma – Perivascular Epitheloid Cell Tumors (PEComa), Recurrent Angiomyolipoma, Lymphangioleiomyomatosis.** Approve for 3 years.

13. **Thymomas and Thymic Carcinomas.** Approve for 3 years if the patient has tried chemotherapy. Note: Examples are cisplatin plus doxorubicin, cisplatin plus etoposide, carboplatin plus paclitaxel.

14. **Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma (WM/LPL).** Approve for 3 years in patients who meet the following criteria (A or B):
    A) Patient has not responded to primary therapy; OR

Note: Examples are Velcade® [bortezomib intravenous or subcutaneous injection] with dexamethasone; Treanda® [bendamustine intravenous], Rituxan combination therapies; Velcade; Velcade with dexamethasone; Kyprolis® [carfilzomib intravenous injection] with Rituxan and dexamethasone; cyclophosphamide/doxorubicin/vincristine/prednisone/Rituxan; Imbruvica® [ibrutinib capsules]; Rituxan.

B) Patient has progressive or relapsed disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Afinitor (generics) and Afinitor Disperz is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Afinitor® tablets, Afinitor Disperz® tablets for oral suspension [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; February 2020.
2. Zortress® tablets [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; January 2018.
3. The NCCN Drugs & Biologics Compendium. © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 25, 2021. Search term: everolimus.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	• Breast Cancer: Criteria were revised to add premenopausal or perimenopausal patients who are receiving ovarian suppression or ablation. Advanced disease was revised to say recurrent, Stage IV, or metastatic disease. Patients with HR-receptor-negative disease with clinical characteristics predicting a HR+ tumor was added as an option. Afinitor use in combination with Faslodex or tamoxifen was added. Afinitor in combination with exemestane continues to be an option in patient with HR+ and HER2-negative breast cancer. The patient has not had disease progression while on Afinitor was added to criteria. • Renal Cell Carcinoma, Advanced: Cabometyx was added to the list of agents tried before receiving Afinitor. • Tuberous Sclerosis Complex (TSC) Associated Partial Onset Seizures: Added new FDA approved use. • Advanced Breast Cancer in Patients with HER2-negative Disease Already Started on Afinitor Therapy. This use was removed. • Endometrial Carcinoma: This condition was added. • Gastrointestinal Stromal Tumors: This condition was added. • Meningioma: This condition was added. • Conditions Not Recommended for Approval: Endometrial Carcinoma and Gastrointestinal Stromal Tumors were removed and added to Other Uses with Supportive Evidence. Chronic Lymphocytic Leukemia, Pancreatic Adenocarcinoma, and Small Cell Lung Cancer were removed.	04/11/2018
Annual Revision	• Breast Cancer: Deleted "metastatic" from criteria describing disease. Re-organized criteria to only approve for HR+/HER2-negative disease. Deleted criteria for HR-negative disease. Added approval for "male" since male with breast cancer treated similar to postmenopausal female. Added gender definition in Policy Statement. Re-worded criteria to state that patient has tried one prior endocrine therapy and listed anastrazole, letrozole, tamoxifen as examples. For Afinitor use in combination with exemestane, added criteria that if the patient is male then gonadotropin-releasing hormone (GnRH) agonist is used. For Afinitor use in combination with Faslodex or Tamoxifen, in males GnRH agonist is not required. • Neuroendocrine Tumors: Added qualifier "of the Pancreas, Gastrointestinal Tract, Lung and Thymus (Carcinoid Tumors" as per guidelines. • Renal Cell Carcinoma: Deleted "advanced" as qualifier. Added "Clear Cell or Non-Clear Cell" to condition as qualifiers. Added criteria to state "relapsed or Stage IV" disease. Deleted criteria separately asking for non-clear cell disease. Modified	05/08/2019

	criteria for clear cell to state "If using for clear cell disease" then "at least one prior systemic therapy" has been tried and listed agents as examples. • Re-worded condition to state Tuberous Sclerosis Complex-"Associated" Renal angiomyolipoma. • Same change to add Tuberous Sclerosis Complex-"Associated" subependymal giant cell astrocytoma. • Osteosarcoma: Deleted criteria since no longer supported in compendium. • Deleted all conditions listed under "Conditions Not Recommended for Approval".	
Selected Revision	• Added generic 2.5 mg, 5 mg, and 7.5 mg tablets to drug target list. No criteria changes.	01/08/2020
Annual Revision	No criteria changes.	05/27/2020

HISTORY (continued)

Early Annual Revision	• Deleted Everolimus tablets 2.5 mg, 5 mg, 7.5 mg from targeted list, since it is already listed next to brand Afinitor. • All throughout policy, where applicable, changed examples to list in Note. • **Hodgkin Lymphoma Classical (nodular sclerosis, mixed cellularity, lymphocyte depleted, and lymphocyte-rich subtypes of Hodgkin lymphoma):** Changed indication name to "Classic Hodgkin Lymphoma" and deleted the subtypes in parentheses to be in-line with other policies with this indication. • **Perivascular Epitheloid Cell Tumors (PEComa), Recurrent Angiomyolipoma, Lymphangioleiomyomatosis.** Added "Soft Tissue Sarcoma" to indication heading to group the subtypes listed under one disease state.	01/27/2021

HR+ – Hormone receptor positive; HR-negative – Hormone receptor negative; HER2 – Human epidermal growth factor 2**.**

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Alecensa® (alectinib capsules – Genentech)

DATE REVIEWED: 02/05/2020

OVERVIEW

Alecensa, a tyrosine kinase inhibitor (TKI), is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic non-small cell lung cancer (NSCLC).[1] Alecensa targets ALK and RET; it also has a major active metabolite, M4, which demonstrated similar *in vitro* potency and activity as alectinib.

GUIDELINES

According to the National Comprehensive Cancer Network (NCCN) NSCLC guidelines (version 2.2020 – December 23, 2019), Alecensa is the category 1preferred therapy for ALK+ NSCLC.[2] Alunbrig™ (brigatinib tablets) and Zykadia™ (ceritinib capsules) are the other recommended, category 1, first-line therapies. , Xalkori® (crizotinib capsules) is a category 1 recommended option "useful in certain circumstances". For subsequent therapy after progression on Xalkori, local therapy, continuing Xalkori therapy, or switching therapy to Zykadia, Alunbrig, or Alecensa (all category 2A) is recommended. For progression on For progression on one of Alecensa, Zykadia, or Alunbrig as first-line therapy, Lorbrena (lorlatinib tablets) can be used upon progression (category 2A).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Alecensa. All approvals are provided for 3 years in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Alecensa is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Non-Small Cell Lung Cancer (NSCLC).** Approve for 3 years if the patient has *metastatic* anaplastic lymphoma kinase (*ALK*)-positive NSCLC as detected by an approved test.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Alecensa has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

193. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

249. Alecensa® capsules [prescribing information]. South San Francisco, CA: Genentech; June 2018.
250. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 2.2020 – December 23, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed January 31, 2020.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	01/20/2016
Annual revision	No criteria changes	01/25/2017
Selected revision	Added approval criteria for first-line setting based on a Phase III trial. Added "after Xalkori therapy" qualifier to indication description for FDA-approved use.	06/14/2017
Annual revision	Deleted approval criteria for "After Xalkori Therapy" since Alecensa is approved in first-line setting. Deleted qualifier "First-Line Therapy" and moved criteria from Other Uses to FDA-Approved Indications. Added "as detected by an approved test" to criteria to check for ALK-positive NSCLC.	01/24/2018
Annual revision	No criteria changes	01/30/2019
Annual revision	No criteria changes	02/05/2020

ALK – Anaplastic lymphoma kinase; NSCLC – Non-small cell lung cancer.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Alunbrig™ (brigatinib tablets – ARIAD/Takeda)

DATE REVIEWED: 06/10/2020

OVERVIEW

Alunbrig, a kinase inhibitor, is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test.[1]

Alunbrig targets *ALK*, c-ros oncogene 1 (*ROS1*), insulin-like growth factor-1 receptor (*IGF-1R*), *FLT-3*, epidermal growth factor receptor (*EGFR*) deletion and point mutations.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on NSCLC (version 5.2020 – May 27, 2020) recommend testing for ALK gene rearrangements in all patients with non-squamous NSCLC (category 1).[2] Testing is a prerequisite before treatment. Alecensa® (alectinib capsules) is the "Preferred" first-line therapy. Alecensa and Zykadia™ (ceritinib capsules) are category 1 recommended regiments under "Other Recommended" first-line therapies. Xalkori® (crizotinib capsules) is a category 1 therapy noted as "useful in certain circumstances". For subsequent therapy with progression on Xalkori, Xalkori can be continued, or therapy can be switched to Alecensa, Alunbrig, or Zykadia if not previously [all category 2A]. For patients who progress on Alecensa, Zykadia, or Alunbrig, local therapy can be considered in addition to continuing the kinase inhibitors or therapy can be switched to Lorbrena (lorlatinib tablets) for multiple systemic lesions.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Alunbrig. All approvals are provided for 3 years in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Alunbrig is recommended in those who meet the following criteria:

FDA-Approved Indications

35. Non-Small Cell Lung Cancer (NSCLC). Approve for 3 years if the patient has *metastatic* NSCLC that is anaplastic lymphoma kinase (*ALK*)-positive as detected by an approved test.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Alunbrig has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

194. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

251. Alunbrig™ tablets [prescribing information]. Cambridge, MA: ARIAD/Takeda Pharmaceuticals; May 2020.
252. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 5.2020 – May 27, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed June 8, 2020.
253. Food and Drug Administration. Lists of cleared or approved companion diagnostic devices (in vitro and imaging tools). Available at: https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools. Accessed on May 21, 2019.

HISTORY

Type of Revision	Summary of Changes*	Date Reviewed

New Policy	--	05/17/2017
Selected revision	Modified criteria for approval in patients who have tried any one of the first-line therapies for ALK-positive non-small cell lung cancer, based on guidelines and reviewer feedback.	07/12/2017
Annual revision	No criteria changes	05/02/2018
Annual revision	The guidelines support the use of Alunbrig first-line for ALK-positive lung cancer. The requirement to have tried another ALK inhibitor for lung cancer prior to Alunbrig approval has been deleted.	05/22/2019
Annual revision	No criteria changes	06/10/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Ayvakit Prior Authorization Policy
- Ayvakit® (avapritinib tablets – Blueprint Medicines)

REVIEW DATE: 02/10/2021

OVERVIEW

Ayvakit, a kinase inhibitor, is indicated for the **treatment** of adults with **unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (*PDGFRA*) exon 18 mutation, including *PDGFRA D842V* mutations**.[1] Patients should be selected for treatment with Ayvakit based on the presence of a *PDGFRA* exon 18 mutation; an FDA-approved test for the detection of this mutation is not currently available.

Guidelines

- **Gastrointestinal stromal tumors (GISTs):** According to the National Comprehensive Cancer Network (NCCN) GISTs guidelines (version 1.2021 – October 30, 2020), Ayvakit is one of the primary treatment options (category 2A) for GIST with *PDGFRA* exon 18 mutation, including *PDGFRA* D842V mutations.[2,3] Imatinib is a category 1 recommended option for primary treatment. The guidelines note that most mutations in the *PDGFRA* gene are associated with a response to imatinib, with the notable exception of *PDGFRA* D842V mutation. Ayvakit is listed as one of the recommended therapies after disease progression on imatinib, Sutent, and Stivarga (regorafenib tablets). Ayvakit (for *PDGFRA* exon 18 mutations that are insensitive to imatinib, including the *D842V* mutation) is listed as a preferred regimen for neoadjuvant therapy for resectable GISTs with significant morbidity. Imatinib is also a preferred regimen for neoadjuvant and adjuvant therapy.
- **Myeloid/Lymphoid Neoplasms with Eosinophilia:** The NCCN guidelines for myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase fusion genes (version 3.2021 – August 21, 2020) notes that since Ayvakit targets *PDGFRA* exon 18 mutation, it may have a role for use in patients with this condition.[3,4] Its use maybe be specific to *PDGFRA* D842V mutation, which is resistant to imatinib. If clinical trial of Ayvakit for this condition is available, then the clinical trial is preferred, rather than off-label use.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ayvakit. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ayvakit is recommended in those who meet the following criteria:

FDA-Approved Indications

47. Gastrointestinal Stromal Tumor (GIST). Approve for 3 years if the patient meets the following criteria (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The tumor is positive for platelet-derived growth factor receptor alpha (*PDGFRA*) exon 18 mutation.
  Note: *PDGFRA* exon 18 mutation includes *PDGFRA D842V* mutations.

Other Uses with Supportive Evidence

2. Myeloid/Lymphoid Neoplasms with Eosinophilia. Approve for 3 years if the patient meets the following criteria (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The tumor is positive for platelet-derived growth factor receptor alpha (*PDGFRA*) *D842V* mutation.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ayvakit is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Ayvakit™ tablets [prescribing information]. Cambridge, MA: Blueprint Medicines Corporation; January 2020.
2. The NCCN Gastrointestinal Stromal Tumors (GISTs) Clinical Practice Guidelines in Oncology (version 1.2021 – October 30, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 18, 2021.
3. The NCCN Drugs & Biologics Compendium. © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 18, 2021. Search term: avapritinib.
4. The NCCN Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase fusion genes Clinical Practice Guidelines in Oncology (version 3.2021 – August 21, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 18, 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/15/2020
Update	3/3/2020: updated with Ayvakit placement in guidelines.	03/03/2020
Annual Revision	**Gastrointestinal Stromal Tumor (GIST):** Added age criterion of ≥ 18 years to define adults. Deleted criteria "patient has unresectable or metastatic disease" since guidelines recommend use of Ayvakit in the neoadjuvant setting. **Myeloid/Lymphoid Neoplasms with Eosinophilia:** Added new approval condition and criteria for this condition based on guidelines.	02/10/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Balversa™ (erdafitinib tablets – Janssen Pharmaceuticals)

DATE REVIEWED: 04/08/2019

OVERVIEW

Balversa is a kinase inhibitor which binds and inhibits the enzymatic activity of fibroblast growth factor receptor (FGFR) 1, FGFR2, FGFR3, and FGFR4, leading to decreased viability in cell lines expressing FGFR genetic alterations.[1] Balversa demonstrated antitumor activity in FGFR expressing cell lines and xenograft models, including bladder cancer.

Balversa is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma that has susceptible FGFR3 or FGFR2 genetic alterations, and progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of adjuvant or neoadjuvant platinum-containing chemotherapy.[1]

Patients are selected for treatment with Balversa based on the presence of susceptible FGFR genetic alterations in tumor specimens detected by an FDA-approved companion diagnostic.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for bladder cancer (version 3.2020 – January 17, 2020) recommend Balversa as a single agent, post-platinum or –checkpoint inhibitor therapy in patients with bladder cancer, upper genitourinary tract tumors, and urothelial carcinoma of the prostate with susceptible FGFR2 or FGFR3 genetic alterations.[2,3]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Balversa. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Balversa is recommended in those who meet the following criteria:

FDA-Approved Indications

132. Urothelial Carcinoma, Locally Advanced or Metastatic. Approve for 3 years if the patient meets the following criteria (A and B):

A) The patient has susceptible fibroblast growth factor receptor 3 or fibroblast growth factor receptor 2 genetic alterations; AND

B) The patient has progressed during or following prior platinum-containing chemotherapy (i.e., cisplatin, oxaliplatin) or checkpoint inhibitor therapy.
Note: Checkpoint inhibitors include: Keytruda® (pembrolizumab injection for intravenous use), Opdivo® (nivolumab injection for intravenous use), Tecentriq® (atezolizumab injection for intravenous use), Imfinzi® (durvalumab injection for intravenous use), and Bavencio® (avelumab injection for intravenous use).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Balversa has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

146. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

463. Balversa™ tablets [prescribing information]. Horsham, PA: Janssen Pharmaceuticals; April 2019.
464. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (Version 3.2020 – January 17, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed April 01, 2020.
465. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on April 01, 2020. Search term: erdafitinib.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/17/2019
Annual Revision	Added checkpoint inhibitor therapy to criteria: The patient has progressed during or following…. or checkpoint inhibitor therapy.	04/08/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Bosulif Prior Authorization Policy

- Bosulif® (bosutinib tablets – Pfizer)

REVIEW DATE: 04/01/2020

OVERVIEW

Bosulif, a tyrosine kinase inhibitor (TKI), is indicated for the treatment of adults with: newly diagnosed chronic phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML).[1] This indication was approved under accelerated approval based on molecular and cytogenetic response rates. Continued approval for this indication may be contingent upon verification and confirmation of clinical benefit in an ongoing long-term follow-up trial. Bosulif is also indicated for the treatment of adults with chronic phase (CP), accelerated phase (AP), or blast phase (BP) Ph+ CML with resistance or intolerance to prior therapy. Currently, there are four other TKIs approved for the treatment of Ph+ CML: Gleevec® (imatinib tablets, generic), Sprycel® (dasatinib tablets), Tasigna® (nilotinib capsules), and Iclusig® (ponatinib tablets).[2-5] These agents are indicated for the treatment of Ph+ CML in various phases; some TKIs are indicated after resistance or intolerance to prior therapy. Iclusig is approved for patients with T315I-positive CML and in adult patients with CML for whom no other TKI therapy is indicated.[5] Sprycel, Gleevec and Iclusig are also indicated for use in patients with Ph+ acute lymphoblastic leukemia (ALL).[2,3,5]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for CML (version 3.2020 – January 30, 2020) state that for patients with CP CML with a low-risk score, the primary treatment recommended includes a first-generation TKI (Gleevec or generic imatinib 400 mg QD [Category 1]), or a second-generation TKI (Bosulif 400 mg QD [Category 1], Sprycel 100 mg QD [Category 1], or Tasigna 300 mg BID [Category 1]).[6] For patients with CP CML with an intermediate- or high-risk score, a second-generation TKI is preferred (Bosulif 400 mg QD [Category 1], Sprycel 100 mg QD [Category 1], or Tasigna 300 mg BID [Category 1]). A first-generation TKI (Gleevec or generic imatinib 400 mg QD) is an alternative [Category 2A]. Iclusig is an option for patients with a T315I mutation and for with disease that has not responded to multiple TKIs or in whom another TKI is not indicated.[6] The NCCN guidelines for ALL (adult and adolescent young adults) [version 1.2020 – January 15, 2020] recommend Bosulif as an option for patients with relapsed or refractory ALL.[7]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Bosulif. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Bosulif is recommended in those who meet the following criteria:

FDA-Approved Indications

36. Chronic Myeloid Leukemia (CML) That is Philadelphia Chromosome Positive (Ph+). Approve for 3 years.

Other Uses with Supportive Evidence

2. Acute Lymphoblastic Leukemia (ALL) That is Philadelphia Chromosome Positive (Ph+). Approve for 3 years if the patient has tried at least one other tyrosine kinase inhibitor (TKI) for Ph+ ALL.
Note: Examples include Gleevec® (imatinib tablets) and Sprycel® (dasatinib tablets).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Bosulif is recommended in those who meet the following criteria:

195. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

254. Bosulif® tablets [prescribing information]. New York, NY: Pfizer Inc; October 2019.
255. Gleevec® tablets [prescribing information]. East Hanover, NJ: Novartis; July 2018.
256. Sprycel® tablets [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; December 2018.
257. Tasigna® capsules [prescribing information]. East Hanover, NJ: Novartis; September 2019.
258. Iclusig® tablets [prescribing information]. Cambridge, MA: Ariad Pharmaceuticals; January 2020.
259. The NCCN Chronic Myeloid Leukemia Clinical Practice Guidelines in Oncology (Version 3.2020 – January 30, 2020. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 17, 2020.
260. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (Version 1.2020 – January 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 17, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	For the indication in CML, changed the criteria to approve the request for 3 years. Previously, use of Bosulif required a trial of one TKI inhibitor indicated for Ph+ CML. Criteria added to approve Bosulif in patients with ALL that is Philadelphia Chromosome Positive (Ph+) if the patient has tried one other TKI for Ph+ ALL (e.g., Gleevec® [imatinib tablets], Sprycel® [dasatinib tablets]). Also, removed the criteria allowing for approval if the patient has been started on Bosulif for an indication or condition addressed as an approval in the Recommended Authorization section (FDA-approved indications or other uses with supportive evidence).	03/07/2018
Annual revision	No criteria changes.	03/20/2019
Annual revision	The following changes were made: **Acute Lymphoblastic Leukemia that is Ph+:** The wording that the patient has tried one other TKI for acute lymphoblastic leukemia was changed to state "at least one" and examples of TKIs were moved from the criteria to a note. **Conditions Not Recommended for Approval:** The condition of breast cancer was removed. The National Comprehensive Cancer Network breast cancer guidelines do not recommend use of Bosulif and there have been no recent literature published regarding this use.	04/01/2020

CML – Chronic myeloid leukemia; TKI(s) – Tyrosine kinase inhibitor(s); Ph+ CML – Philadelphia chromosome positive chronic myeloid leukemia; ALL Acute lymphoblastic leukemia; Ph+ – Philadelphia chromosome positive; Ph+ ALL – Philadelphila chromosome positive acute lymphoblastic leukemia.

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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Braftovi Prior Authorization Policy
- Braftovi® (encorafenib capsules – Array BioPharma)

REVIEW DATE: 07/08/2020

OVERVIEW

Braftovi, a BRAF inhibitor, is indicated for the following uses:[1]

- **Melanoma**, in combination with Mektovi® (binimetinib tablets), for the treatment of patients with unresectable or metastatic disease and a *BRAF V600E* or *V600K* mutation, as detected by an FDA-approved test.
- **Colorectal cancer**, in combination with Erbitux® (cetuximab infusion), for the treatment of adults with metastatic disease and a *BRAF V600E* mutation, as detected by an FDA-approved test, after prior therapy.

It is a limitation of use that Braftovi is not indicated for wild-type disease.

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines support use of Braftovi in the following cancers.

- **Melanoma:** Guidelines (version 3.2020 – May 18, 2020) recommend BRAF/MEK inhibitor combinations for first-line (preferred if clinically needed for early response) and subsequent treatment of metastatic or unresectable melanoma with a *V600* activating mutation.[2] While combination BRAF/MEK inhibition is preferred, if a combination is contraindicated, monotherapy with a BRAF inhibitor (Tafinlar® [dabrafenib capsules] or Zelboraf® [vemurafenib tablets]) is a recommended option, particularly if the patient is not a candidate for checkpoint immunotherapy. Following resection of limited metastatic disease with a *BRAF V600*-activating mutation, BRAF/MEK combination therapy is among the treatment options for patients with no evidence of disease. Tafinlar + Mekinist® (trametinib tablets) is also recommended in guidelines as adjuvant therapy (including for nodal recurrence) in some patients with Stage III disease, including use post-surgery or use after complete lymph node dissection. If unacceptable toxicity to Tafinlar/Mekinist, other BRAF/MEK combinations can be considered.
- **Colon and Rectal Cancer:** Guidelines for colon cancer (version 4.2020 – June 15, 2020) and rectal cancer (version 6.2020 – June 25, 2020) recommend Braftovi for some situations in patients with *BRAF-V600E* mutated disease.[3,] For primary treatment (following adjuvant chemotherapy) or as subsequent use, Braftovi + Erbitux or Vectibix® (panitumumab IV infusion) is a recommended treatment option.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Braftovi. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Braftovi is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Melanoma.** Approve for 3 years if the patient meets BOTH of the following (A and B):
   - **A)** Patient has unresectable, advanced, or metastatic melanoma; AND
   - **B)** Patient has *BRAF V600* mutation-positive disease.

2. **Colon or Rectal Cancer.** Approve for 3 years if the patient meets the following (A, B, and C):
   - **2.** Patient has *BRAF V600E* mutation-positive disease; AND
   - **3.** Patient has previously received a chemotherapy regimen for colon or rectal cancer; AND
     Note: Examples of chemotherapy regimens include a fluoropyrimidine such as 5-fluorouracil (5-FU), capecitabine; oxaliplatin, irinotecan, or an adjunctive chemotherapy regimen such as FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).
   - **4.** The agent is prescribed as part of a combination regimen for colon or rectal cancer.
     Note: Examples of combination regimens include Braftovi + Erbitux (cetuximab IV infusion), Braftovi + Vectibix (panitumumab IV infusion).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Braftovi is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

261. Braftovi capsules [prescribing information]. Boulder, CO: Array BioPharma; April 2020.
262. The NCCN Melanoma Clinical Practice Guidelines in Oncology (Version 3.2020 – May 18, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 2, 2020.
263. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 4.2020 – June 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 2, 2020.
264. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (Version 6.2020 – June 25, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 2, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	06/27/2018
Annual revision	**Colon or Rectal Cancer:** Add criteria as supported by NCCN colon cancer guidelines. Criteria approve if the patient has *BRAF V600E* mutation-positive disease, and if the patient has previously used chemotherapy, and if Braftovi will be used as part of a combination regimen for colon or rectal cancer.	06/18/2019
Update	**04/10/2020:** Update Overview with information for colon or rectal cancer. Move colon or rectal cancer to FDA-approved uses (previously addressed in Other Uses With Supportive Evidence). No changes to the criteria.	--
Annual revision	**Colon or Rectal Cancer:** Update examples to remove Mektovi from the examples of combination regimens.	07/08/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Brukinsa Prior Authorization Policy

- Brukinsa™ (zanubrutinib capsules – BeiGene)

REVIEW DATE: 06/03/2020; selected revision 01/20/2021

OVERVIEW

Brukinsa, a Bruton's tyrosine kinase inhibitor (BTK), is indicated for the treatment of **mantle cell lymphoma,** in adults who have received at least one prior therapy.[1]

Disease Overview

Mantle cell lymphoma is a rare and fasting-growing type of non-Hodgkin lymphoma (NHL).[2,3] It accounts for approximately 3% of cases of newly diagnosed NHL. The condition is described as aggressive and non-curable. It is defined by the overexpression of cyclin D1. The median age at diagnosis is 68 years of age and it is more common in males. Mantle cell lymphoma is a cancer involving the lymphatic system which is part of the immune system comprised of lymph tissue, lymph nodes, the spleen, thymus, tonsils, and bone marrow. About 15% to 30% of patients have involvement of the gastrointestinal tract. Approximately one-third of patients with mantle cell lymphoma present with high levels of lactate dehydrogenase (LDH). Although there is no definitive standard of care, aggressive chemo-immunotherapy regimens containing rituximab and cytarbine are used for patients depending on fitness. Many targeted therapies are now available. Stem cell transplants is also an option.

Chronic lymphocytic leukemia (CLL) is one of the most prevalent adult leukemias in the Western world.[4] In 2019, an estimated 20,720 patients will be diagnosed with CLL in the US, and approximately 3,930 patients will die from the disease. The condition usually is diagnosed in older adults (≥ 70 years of age) and occurs more frequently in men. The leukemic cells appear as small, mature lymphocytes. CLL and small lymphocytic lymphoma (SLL) are different manifestations of the same condition and are managed similarly. In CLL, many of the abnormal lymphocytes are found in the blood, as well as in the bone marrow and lymphoid tissue. In SLL, there are few, if any, abnormal lymphocytes circulating in blood and most of the disease is in the lymph nodes, bone marrow, and other lymphoid tissue. The diagnosis requires the presence of at least 5×10^9/L monoclonal B-lymphocytes in the peripheral blood. SLL requires the presence of lymphadenopathy and/or splenomegaly with $< 5 \times 10^9$/L B-lymphocytes found in the peripheral blood.

Guidelines

Several guidelines address use of Brukinsa.

- **Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)**:[4] The National Comprehensive Cancer Network (NCCN) guidelines for CLL/SLL (version 2.2021 – December 3, 2020) recommend Brukinsa as an option for second-line and subsequent therapy for patients without 17p deletion/TP53 mutation who are frail patients with significant comorbidity or patients < 65 years of age without significant comorbidities who have intolerance or contraindication to other BTK inhibitors (category 2A). For patients with 17p deletion/TP53 mutation, Brukinsa is recommended as a first-line therapy as an other recommended regimen for patients with a contraindication to other BTK inhibitors (category 2A). Also, for this population, Brukinsa is recommended as second-line and subsequent therapy as an other recommended regimen for patients with intolerance or a contraindication to other BTK inhibitors (category 2A).
- **Mantle Cell Lymphoma:**[2] The NCCN guidelines for B-cell lymphomas (version 4.2020 – August 13, 2020) address mantle tell lymphoma. Brukinsa is recommended as a preferred regimen among several as second-line therapy for patients with short response duration to prior chemoimmunotherapy, as well as for extended response duration prior to chemoimmunotherapy (category 2A).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Brukinsa. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Brukinsa is recommended in those who meet the following criteria:

FDA-Approved Indication

133. Mantle Cell Lymphoma. Approve for 3 years if the patient has tried at least one prior therapy.
Note: Example of therapies are Calquence® (acalabrutinib capsules); Imbruvica® (ibrutinib tablets and capsules) with or without a rituximab product; Revlimid® (lenalidomide capsules) with or without a rituximab product; Venclexta® (venetoclax tablets) with or without a rituximab product; RDHA (a rituximab product, dexamethasone, cytarabine) plus platinum (carboplatin, cisplatin, oxaliplatin); alternating RCHOP (a rituximab product, cyclophosphamide, doxorubin, vincristine, prednisone)/RDHAP (a rituximab product, dexamethasone, cytarbine, cisplatin); Treanda® (bendamustine injection) plus a rituximab product; RCHOP; NORDIC regimen (dose-intensified induction immunochemotherapy with ritixumab plus cyclophosphamide, vincristine, doxorubicin, prednisone [maxi-CHOP]) alternating with a rituximab product plus high-dose cytarbine); HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamathsone alternating with high-dose methotrexate and cytarabine plus rituximab); and VR-CAP (Velcade® [bortezomib injection for subcutaneous or intravenous use], a rituximab product, cyclophosphamide, doxorubicin, and prednisone).

Other Uses with Supportive Evidence

134. Chronic Lymphocytic Leukemia. Approve for 3 years if the patient has tried at least one prior therapy.
Note: Example of therapies are Imbruvica® (ibrutinib tablets and capsules); Calquence® (acalabrutinib capsules); Copiktra® (duvelisib capsules); Gazyva® (obinutuzumab injection for intravenous use); Calquence with Gazyva; Venclexta® (venetoclax tablets) with Gazyva; Imbruvica with Gazyva; Venclexta with rituximab; Zydelig® (idelalisib tablets); and Zydelig plus rituximab.

135. Small Lymphocytic Lymphoma. Approve for 3 years if the patient has tried at least one prior therapy.
Note: Example of therapies are Imbruvica® (ibrutinib tablets and capsules); Calquence® (acalabrutinib capsules); Copiktra® (duvelisib capsules); Gazyva® (obinutuzumab injection for intravenous use); Calquence with Gazyva; Venclexta® (venetoclax tablets) with Gazyva; Imbruvica with Gazyva; Venclexta with rituximab; Zydelig® (idelalisib tablets); and Zydelig plus rituximab.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Brukinsa is not recommended in the following situations:

196. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

244. Brukinsa™ capsules [prescribing information]. San Mateo, CA: BeiGene; November 2019.
245. The NCCN B-cell Lymphomas Guidelines in Oncology (version 4.2020 – August 13, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 17, 2021.
246. Maddocks K. Update on mantle cell lymphoma. *Blood*. 2018;132(16):1647-1656.
247. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (version 4.2021 – December 3, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at http://www.nccn.org. Accessed on January 17, 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	---	11/20/2019
Update	12/2/2019: No criteria changes. Overview changed to include updated National Comprehensive Cancer Network guidelines for B-Cell Lymphomas.	--
Update	12/22/2020: No criteria changes. Overview changed to include updated National Comprehensive Cancer Network guidelines for B-Cell Lymphomas	--
Early Annual Revision	No criteria changes.	06/03/2020
Selected Revision	**Chronic Lymphocytic Leukemia:** Criteria added to approve for 3 years if the patient has tried at least one prior therapy. Examples of therapies are provided in a Note. **Small Lymphocytic Lymphoma.** Criteria added to approve for 3 years if the patient has tried at least one prior therapy. Examples of therapies are provided in a Note.	01/20/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Cabometyx Prior Authorization Policy

- Cabometyx™ (cabozantinib tablets – Exelixis)

REVIEW DATE: 02/17/2021

OVERVIEW

Cabometyx, a kinase inhibitor, is indicated for the following uses:[1]

- **Renal cell carcinoma (RCC)**, as monotherapy or in combination with Opdivo (nivolumab for injection) for the first-line treatment of patients with advanced disease.
- **Hepatocellular carcinoma,** for the treatment of patients who have been previously treated with Nexavar® (sorafenib tablets).

Guidelines

- **Renal cell carcinoma (RCC):** In the National Comprehensive Cancer Network (NCCN) clinical practice guidelines for kidney cancer (version 2.2021 – February 3, 2021), the preferred regimens for first-line therapy in favorable risk patients with relapsed or Stage IV RCC with predominant clear cell histology are: Inlyta® (axitinib tablets) + Keytruda (pembrolizumab for injection), Cabometyx + Opdivo (nivolumab for injection), Sutent® (sunitinib malate capsules), and Votrient® (pazopanib tablets) [all category 2A]. Cabometyx (category 2B) is one of the "other recommended regimens" for favorable risk patients.[2] For patients in the poor/intermediate risk grouping, the preferred regimens are Inlyta + Keytruda; Yervoy (ipilimumab for injection) + Opdivo (both category 1); Cabometyx; and Cabometyx + Opdivo (both category 2A). Recommendations for subsequent oral therapies include Cabometyx (category 1, preferred), Inlyta (category 1),

Lenvima™ (lenvatinib capsules) + everolimus [category 1]; everolimus, Sutent, or Votrient are all category 2A recommended therapies. For patients with non-clear cell histology RCC, Sutent and enrollment in clinical trials are noted as preferred therapies (category 2A, preferred); Cabometyx, everolimus, and Lenvima + everolimus are other recommended regimens (both category 2A). Many other agents are listed as useful in certain circumstances.

- **Hepatocellular carcinoma:** The NCCN hepatobiliary cancers (version 5.2020 – August 4, 2020) recommends Cabometyx (Child-Pugh Class A only; Category 1) as a subsequent therapy option, along with many other agents.[3]
- **Non-small cell lung cancer:** The NCCN Non-Small Cell Lung Cancer guidelines (version 3.2021 – February 16, 2021) recommend cabozantinib as "useful in certain circumstances" for *RET* rearrangements (category 2A).[4,5]
- **Gastrointestinal stromal tumors (GIST):** The NCCN GISTs guidelines (version 1.2021 – October 30, 2020) recommend Cabometyx as one of the options after failure on approved therapies ("useful in certain circumstances", category 2A).[4,6] The approved therapies are imatinib and Ayvakit (avapritinib tablets; for *PDGFRA* mutation) first-line; Sutent (sunitinib capsules) as second-line therapy; Stivarga (regorafenib tablets) as third-line therapy; and Gavreto (ripretinib tablets) as fourth-line therapy.
- **Bone cancer:** The NCCN bone cancer guidelines (version 1.2021 – November 20, 2020) recommend Cabometyx as one of the "other recommended regimens" for second-line (relapsed/refractory or metastatic disease) Ewing sarcoma (category 2A).[4,7]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cabometyx. All approvals are provided for 3 years in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cabometyx is recommended in those who meet the following criteria:

FDA-Approved Indication

37. Renal Cell Carcinoma (RCC). Approve for 3 years in patients with relapsed or stage IV disease.

2. Hepatocellular Carcinoma. Approve for 3 years if the patient has been previously treated with at least one tyrosine kinase inhibitor therapy.
Note: Examples are Nexavar® (sorafenib tablets), Lenvima (lenvatinib capsules).

Other Uses with Supportive Evidence

3. Non-Small Cell Lung Cancer. Approve for 3 years if the tumor is positive for *RET* rearrangements.

4. Gastrointestinal Stromal Tumors (GIST). Approve for 3 years if the patient meets the following (A and B):
- **A)** Patient has previously tried one of imatinib (Gleevec® tablets, generic) or Ayvakit® (avapritinib tablets); AND
- **B)** Patient has previously tried each of Sutent® (sunitinib capsules), Stivarga® (regorafinib tablets), and Gavreto (ripretinib tablets).

5. Bone Cancer. Approve for 3 years if the patient meets the following criteria (A and B):
- **A)** Patient meets ONE of the following (i or ii):
  - **i.** Patient has Ewing sarcoma; OR
  - **ii.** Patient has osteosarcoma; AND
- **B)** Patient has tried at least one previous systemic regimen.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cabometyx is not recommended in the following situations:

1. Metastatic Castration-Resistant Prostate Cancer (mCRPC).
Results from the COMET-1 Phase III pivotal study with Cabometyx 60 mg tablets in men with mCRPC are published.[8] Patients included in the study had disease progression after treatment with docetaxel as well as Zytiga® (abiraterone acetate tablets) and/or Xtandi® (enzalutamide capsules). The study failed to meet its primary endpoint of demonstrating statistically significant increase in overall survival (OS) compared with prednisone. The median OS with Cabometyx was 11.0 months vs. 9.8 months with prednisone (hazard ratio [HR] 0.90; 95% CI: 0.76, 1.06; P = 0.213). Based on these results, the second Phase III study, COMET-2 has been discontinued.[9]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

248. Cabometyx™ [prescribing information]. San Francisco, CA: Exelixis Inc; February 2021.
249. The NCCN Kidney Cancer Clinical Practice Guidelines in Oncology (version 2.2021 – February 3, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed February 8, 2021.
250. The NCCN Hepatobiliary Cancers Clinical Practice Guidelines in Oncology (version 5.2020 – August 4, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed February 17, 2021.
251. The NCCN Drugs & Biologics Compendium. © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 14, 2021. Search term: cabozantinib.
252. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2021 – February 16, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed February 17, 2021.
253. The NCCN Gastrointestinal Stromal Tumors (GISTs) Clinical Practice Guidelines in Oncology (version 1.2021 – October 30, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed February 17, 2021.
254. The NCCN Bone Cancer Clinical Practice Guidelines in Oncology (version 1.2021 – November 20, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed February 17, 2021.
255. Smith M, De Bono J, Sternberg C, et al. Phase III study of cabozantinib in previously treated metastatic castration-resistant prostate cancer: COMET-1. *J Clin Oncol.* 2016;34:3005-3013.
256. Exelixis. Study of cabozantinib (XL184) versus mitoxantrone plus prednisone in men with previously treated symptomatic castration-resistant prostate cancer (COMET-2). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2017 April 18]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01522443?term=NCT01522443&rank=1. NLM identifier: NCT01522443 (terminated).

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Added new approval condition for hepatocellular carcinoma based on FDA-approval.	01/23/2019
Annual Revision	No criteria changes	02/05/2020
Annual Revision	**Renal Cell Carcinoma:** Deleted "Advanced, (Predominant Clear Cell or Non-Clear Histology)" from indication heading. Criterion was modified to approve for 3 years "in patients with relapsed or stage IV disease", in-line with guidelines. **Hepatocellular Carcinoma:** Moved examples from within criteria to a Note. **Non-Small Cell Lung Cancer:** Deleted "with RET Gene Arrangements" from indication and moved it to criteria. Now, criteria approves "if the tumor is positive for RET rearrangements". **Gastrointestinal Stromal Tumors (GIST):** Added new approval condition and criteria based on guidelines. **Bone Cancer:** Added new approval condition and criteria for bone cancer, specifically for Ewing sarcoma and osteosarcoma, based on guidelines.	02/17/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Calquence Prior Authorization Policy

- Calquence® (acalabrutinib capsules – Astra Zeneca)

REVIEW DATE: 06/03/2020; selected revision 01/20/2021

OVERVIEW

Calquence, a Bruton tyrosine kinase (BTK) inhibitor, is indicated for the following uses:[1]

- **Chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL)**, in adults.
- **Mantle cell lymphoma**, in adults who have received at least one prior therapy active disease.

Disease Overview

CLL is one of the most prevalent adult leukemias in the Western world.[2] In 2019, an estimated 20,720 patients will be diagnosed with CLL in the US, and approximately 3,930 patients will die from the disease. The condition usually is diagnosed in older adults (≥ 70 years of age) and occurs more frequently in men. The leukemic cells appear as small, mature lymphocytes. CLL and SLL are different manifestations of the same condition and are managed similarly. In CLL, many of the abnormal lymphocytes are found in the blood, as well as in the bone marrow and lymphoid tissue. In SLL, there are few, if any, abnormal lymphocytes circulating in blood and most of the disease is in the lymph nodes, bone marrow, and other lymphoid tissue. The diagnosis requires the presence of at least 5×10^9/L monoclonal B-lymphocytes in the peripheral blood. SLL requires the presence of lymphadenopathy and/or splenomegaly with $< 5 \times 10^9$/L B-lymphocytes found in the peripheral blood.

Mantle cell lymphoma is a rare and fasting-growing type of non-Hodgkin lymphoma (NHL).[3] It accounts for approximately 6% of cases of newly-diagnosed NHL. The median age at diagnosis is 68 years of age and it is more common in males. Mantle cell lymphoma is a cancer involving the lymphatic system which is part of the immune system comprised of lymph tissue, lymph nodes, the spleen, thymus, tonsils, and bone marrow. Approximately one-third of patients with mantle cell lymphoma present with high levels of lactate dehydrogenase.

Waldenstrom's macroglobulinemia is a B-cell disorder that is hallmarked by bone marrow infiltration with lymphophasmacytic cells, as well as with immunoglobulin M monoclonal gammopathy.[4] The condition is defined as "lymphplasmacytic lymphoma" by the Revised European American Lymphoma and World Health Organization classification systems. There are approximately 1,000 to 1,500 new cases of Waldenstrom's macroglobulinemia diagnosed each year in the US. The condition is observed primarily in older adults as the median age at the time of diagnosis ranges from 60 to 75 years. Some symptoms which necessitate treatment include hyperviscosity; neuropathy; anemia; cytopenia and amyloidosis.

Guidelines

Several guidelines address Calquence.

- **CLL/SLL:** The National Comprehensive Cancer Network (NCCN) guidelines for CLL/SLL (version 4.2021 – December 3, 2020) list Calquence as a preferred option as first-line therapy, as well as for relapsed/refractory therapy, in variety of clinical scenarios in patients with and without del(17p)/TP53 mutation.[2] In some clinical scenarios, Calquence is recommended to be given with Gazyva® (obinutuzumab injection for intravenous use).
- **Mantle Cell Lymphoma:** The NCCN guidelines for B-cell lymphomas (version 1.2020 – January 22, 2020) provide recommendations for patients with mantle cell lymphoma.[3] Calquence is recommended as one of several preferred agents as second-line therapy in various clinical scenarios (category 2A).
- **Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma:** The NCCN guidelines for Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma recommend Calquence as an Other Recommended Regimen for previously treated disease (category 2A).[4]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Calquence. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Calquence is recommended in those who meet the following criteria:

FDA-Approved Indications

38. Mantle Cell Lymphoma. Approve for 3 years.

39. Chronic Lymphocytic Leukemia (CLL). Approve for 3 years.

40. Small Lymphocytic Lymphoma (SLL). Approve for 3 years.

Other Uses with Supportive Evidence

41. Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma. Approve for 3 years if the patient has tried at least one prior therapy.
Note: Examples of therapies include Imbruvica® (ibrutinib tablets and capsules) with or without rituximab; Treanda® (bendamustine injection for intravenous infusion); rituximab; rituximab/cyclophosphamide/dexamethasone; Velcade® (bortezomib injection for subcutaneous or intravenous use)/dexamethasone/rituximab; Velcade with or without rituximab; Velcade/dexamethasone; and fludarabine with or without rituximab.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Calquence is not recommended in the following situations:

197. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

237. Calquence® capsules [prescribing information]. Wilmington, DE: AstraZeneca; November 2019.
238. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (Version 4.2021 – December 3, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at http://www.nccn.org. Accessed on January 17, 2021.
239. The NCCN B-cell Lymphomas Guidelines in Oncology (version 1.2020 – January 22, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 28, 2020.
240. The NCCN Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma Clinical Practice Guidelines in Oncology (version 1.2021 – September 1, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at http://www.nccn.org. Accessed on January 18, 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	For clarity, the reference to Rituxan when listing previous required therapies was changed to "rituximab". Also, the following changes were also made: 1. **Chronic Lymphocytic Leukemia:** Venclexta plus Gazyva and Copiktra were added to the list of examples of agents that count toward the requirement of a trial of one prior therapy. 2. **Small Lymphocytic Lymphoma:** Venclexta plus Gazyva and Copiktra were added to the list of examples of agents that count toward the requirement of a trial of one prior therapy.	06/05/2019
Selected Revision	The indications of chronic lymphocytic leukemia and small lymphocytic lymphoma were moved from the Other Uses with Supportive Evidence section to the FDA-	12/4/2019

	Approved Indications section. Also, the criteria were revised to approve for these indications and a trial of one prior therapy is no longer required.	
Annual Revision	No criteria changes.	06/03/2020
Selected Revision	**Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma:** Criteria added to approve if the patient has tried at least one prior therapy. Examples of therapies are provided in a Note.	01/20/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Caprelsa® (vandetanib tablets – AstraZeneca)

DATE REVIEWED: 05/13/2020

OVERVIEW

Caprelsa is a kinase inhibitor indicated for the treatment of symptomatic or progressive medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease.[1] Due to the treatment related risks of Caprelsa, its use in patients with indolent, asymptomatic, or slowly progressing disease should be carefully considered. Caprelsa has a black box warning regarding the increased risk of QT prolongation, Torsades de pointes, and sudden death. It is available only through the restricted distribution program called the Caprelsa Risk Evaluation and Mitigation Strategy (REMS) program. Only prescribers and pharmacies certified with the program are able to prescribe or dispense Caprelsa.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for thyroid carcinoma (version 2.2019 – September 16, 2019) lists surgery as the main treatment option for MTC.[2-3] For *locoregional* , recurrent or persistent disease, or for distant metastases Caprelsa (category 1) or Cometriq™ (cabozantinib capsules) (category 1) are recommended for unresectable locoregional disease that is symptomatic or structurally progressive. The guidelines recommend that Caprelsa be considered if clinical trials or other systemic therapies are not available or appropriate for the treatment of progressive and/or symptomatic iodine refractory thyroid cancer that is unresectable recurrent or persistent locoregional disease or that is distant metastatic disease.[2-3] This recommendation is for follicular, Hürthle cell, and papillary cancer subtypes (all category 2A).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Caprelsa. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Caprelsa is recommended in those who meet the following criteria:

Food and Drug Administration (FDA)-Approved Indications

42. Medullary Thyroid Cancer (MTC). Approve for 3 years.

Other Uses with Supportive Evidence

2. **Differentiated (i.e., papillary, follicular, and Hürthle) Thyroid Carcinoma.** Approve for 3 years if the disease is refractory to radioactive iodine therapy.

3. **Non-Small Cell Lung Cancer with RET Gene Rearrangements.** Approve for 3 years.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Caprelsa has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

198. **Non-Small Cell Lung Cancer (NSCLC) [Without RET Gene Rearrangements].** The efficacy of Caprelsa for the treatment of NSCLC was evaluated in four Phase III studies; three of these studies did not show any statistically significant improvement with Caprelsa with regards to progression free survival (PFS) or overall survival. In the ZEST (Zactima Efficacy Study versus Tarceva) study, Caprelsa was compared with Tarceva® (erlotinib tablets) in patients (n = 1,240) with advanced NSCLC who have had treatment failure with one or two prior cytotoxic chemotherapy regimens.[6] There was no significant improvement in PFS in patients treated with Caprelsa vs. Tarceva (median PFS 2.6 months vs. 2.0 months, respectively; P = 0.721). In the second Phase III study (ZEPHYR), Caprelsa was assessed for overall survival benefit in patients with locally advanced or metastatic NSCLC who have had treatment failures with one or two previous chemotherapy regimens, including an EGFR tyrosine kinase inhibitor.[7] Patients (n = 924) were randomized 2:1 to receive either Caprelsa 300 mg/day or placebo. There was no statistically significant difference in the primary end point of overall survival in patients receiving Caprelsa or placebo. The median overall survival was 8.5 months for Caprelsa and 7.8 months with placebo (P = 0.527). The estimated percentage of patients alive after 1 year was 35.5% vs. 31.7% for Caprelsa and placebo, respectively. In the ZODIAC (Zactima in cOmbination with Docetaxel In non-smAll cell lung Cancer) Phase III study, Caprelsa in combination with docetaxel was compared with placebo and docetaxel in patients (n = 1,391) with locally advanced or metastatic NCSLC after progression following platinum-based first-line chemotherapy.[8] PFS was statistically significant in the Caprelsa group compared with the placebo group for the overall population (median PFS 4.0 months with Caprelsa vs. 3.2 months with placebo; P < 0.0001). There were no significant differences between the two groups for the secondary endpoint of overall survival. In the ZEAL (Zactima Efficacy with Alimta in Lung cancer) study the efficacy of Caprelsa was assessed in combination with Alimta® (pemetrexed disodium injection) for the second-line treatment of patients with advanced NSCLC.[9] The primary efficacy endpoint of PFS was not statistically significantly different between the treatment groups. The median PFS was 17.6 weeks for Caprelsa and 11.9 weeks for placebo (P = 0.108). There were also no significant differences between the two groups for overall survival.

199. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

257. Caprelsa® [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; July 2016.
258. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (Version 2.2019 – September 16, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 11, 2020.
259. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 11, 2020. Search term: vandetanib.
260. Natale RB, Thongprasert S, Greco FA, et al. Phase III trial of vandetanib compared with erlotinib in patients with previously treated advanced non-small-cell lung cancer. *J Clin Oncol.* 2011;29:1059-1066.
261. Lee JS, Hirsh V, Park K, et al. Vandetanib versus placebo in patients with advanced non-small-cell lung cancer after prior therapy with an epidermal growth factor receptor tyrosine kinase inhibitor: a randomized, double-blind Phase III trial (ZEPHYR). *J Clin Oncol.* 2012;30:1114-1121.

262. Herbst RS, Sun Y, Eberhardt WEE, et al. Vandetanib plus docetaxel versus docetaxel as second-line treatment for patients with advanced non-small-cell lung cancer (ZODIAC): a double-blind, randomised, phase 3 trial. *Lancet Oncol.* 2010;11:619-626.
263. De Boer RH, Arrieta O, Yang CH, et al. Vandetanib plus pemetrexed for the second-line treatment of advanced non-small-cell lung cancer: a randomized, double-blind phase III trial. *J Clin Oncol.* 2011;29:1067-1074.

HISTORY

Type of Revision	Summary of Changes*	Date Reviewed
Annual revision	Added new approval indication for Non-Small Cell Lung Cancer with RET Gene Rearrangements based on guidelines. Added clarification to Non-Small Cell Lung Cancer under "Conditions Not Recommended for Approval" that it applies to patients "(Without RET Gene Rearrangements)".	03/15/2017
Annual revision	Deleted the following conditions from Conditions Not Recommended for Approval section due to lack of data in past few years: breast cancer, hepatocellular cancer, ovarian cancer, prostate cancer, and urothelial cancer.	04/11/2018
Annual revision	No criteria changes	04/17/2019
Annual revision	No criteria changes	05/13/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Cometriq™ (cabozantinib capsules – Exelixis Inc.)

DATE REVIEWED: 05/13/2020

OVERVIEW

Cometriq is a kinase inhibitor indicated for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC).[1] *In vitro* biochemical and cellular assays have shown Cometriq to inhibit the tyrosine kinase activity of rearranged during transfection (RET), MET, vascular endothelial cell growth factor receptor (VEGFR)-1, -2, and -3, KIT, tyrosine-related kinase B (TrkB), Fms-like tyrosine kinase 3 (FLT-3), AXL, and TIE-2.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for thyroid carcinoma (version 2.2019 – September 16, 2019) lists surgery as the main treatment option for MTC.[2-3] For *locoregional* , recurrent or persistent disease, or for distant metastases Caprelsa® (vandetanib tablets) [category 1] or Cometriq (category 1) are recommended for unresectable locoregional disease that is symptomatic or structurally progressive. The guidelines recommend that Cometriq be considered if clinical trials or other systemic therapies are not available or appropriate for the treatment of progressive and/or symptomatic iodine refractory thyroid cancer that is unresectable recurrent or persistent locoregional disease or that is distant metastatic disease.[2-3] This recommendation is for follicular, Hürthle cell, and papillary cancer subtypes (all category 2A).

The NCCN Compendium recommends the use of cabozantinib for RET gene rearrangements in non-small cell lung cancer (category 2A).[3]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Cometriq. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cometriq is recommended in those who meet the following criteria:

FDA-Approved Indication

43. Medullary Thyroid Cancer (MTC). Approve for 3 years.

Other Uses with Supportive Evidence

44. Non-Small Cell Lung Cancer with RET Gene Rearrangements. Approve for 3 years.

45. Differentiated (i.e., papillary, follicular, and Hürthle) Thyroid Carcinoma. Approve for 3 years if the disease is refractory to radioactive iodine therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Cometriq has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Metastatic Castration-Resistant Prostate Cancer (mCRPC).** Results from the COMET-1 Phase III pivotal study with cabozantinib 60 mg tablets in men with mCRPC are published.[8] Patients included in the study had disease progressed after treatment with docetaxel as well as Zytiga® (abiraterone acetate tablets) and/or Xtandi® (enzalutamide capsules). The study failed to meet its primary endpoint of demonstrating statistically significant increase in overall survival (OS) compared with prednisone. The median OS with cabozantinib was 11.0 months vs. 9.8 months with prednisone (hazard ratio [HR] 0.90; 95% CI: 0.76, 1.06; P = 0.213). Based on these results, the second Phase III study, COMET-2 has been discontinued.[9]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

264. Cometriq™ [prescribing information]. San Francisco, CA: Exelixis Inc; January 2020.
265. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (Version 2.2019 – September 16, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 11, 2020.
266. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 11, 2020. Search term: cabozantinib.
267. Smith M, De Bono J, Sternberg C, et al. Phase III study of cabozantinib in previously treated metastatic castration-resistant prostate cancer: COMET-1. *J Clin Oncol.* 2016;34:3005-3013.
268. Exelixis. Study of cabozantinib (XL184) versus mitoxantrone plus prednisone in men with previously treated symptomatic castration-resistant prostate cancer (COMET-2). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2017 March 13]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01522443?term=NCT01522443&rank=1. NLM identifier: NCT01522443.
269. Cabanillas ME, de Souza JA, Geyer S, et al. Cabozantinib as salvage therapy for patients with tyrosine kinase inhibitor-refractory differentiated thyroid cancer: results of a multicenter Phase II International Thyroid Oncology Group Trial. *J Clin Oncol.* 2017;35:3315-3321.

HISTORY

Type of Revision	Summary of Changes*	Date Reviewed
Annual revision	No criteria changes	03/15/2017
Annual revision	Added new approval condition for use in Differentiated thyroid cancer under Other Uses with Supportive Evidence, based on guidelines/compendium.	04/11/2018
Annual revision	No criteria changes	04/17/2019
Annual revision	No criteria changes	05/13/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Copiktra Prior Authorization Policy
- Copiktra® (duvelisib capsules – Verastem)

REVIEW DATE: 11/04/2020

OVERVIEW

Copiktra, a kinase inhibitor, is indicated for the treatment of adults with:[1]
- **Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma** (SLL), relapsed or refractory, after at least two prior therapies.
- **Follicular lymphoma**, relapsed or refractory, after at least two prior systemic therapies.

Disease Overview

CLL is one of the most prevalent adult leukemias in the Western world, with an age-adjusted incidence of 4 to 5 per 100,000.[2,3] In 2019, an estimated 20,720 patients were diagnosed with CLL in the US, and around 3,930 patients will die from the disease.[3] The median age at diagnosis is 72 years of age and men are more affected than women (2:1).[2] Lymphadenopathy may be a finding upon presentation, as well as symptoms such as fevers, night sweat, weight loss, or fatigue.[2,3] CLL and SLL are different manifestations of the same condition but managed similarily.[3] Both diseases are characterized by a progressive accumulation of leukemic cells, which appear as small mature lymphocytes and may be found among occasional larger or atypical cells, in the peripheral blood, bone marrow, and lymphoid tissues. One major distinction is that in CLL, a significant number of the abnormal lymphocytes are present in blood, in addition to bone marrow and lymphoid tissue. Comparably, in SLL there are few, if any, abnormal lymphocytes circulating in blood. The bulk of the disease is in the lymph nodes, bone marrow, and in other lymphoid tissue. Many patients with CLL have cytogenetic abnormalities which can serve as markers that provide prognostic information. Drug therapy for CLL is not curative and is often not necessary in uncomplicated early disease. Some patients can be monitored without therapy until they have progressive or symptomatic/active disease. Many medications and therapy regimens are used to manage CLL. Factors to consider for recommending the most optimal regimen for a patient include disease stage, patient symptoms, fitness and other concomitant illnesses of the patient, genetic factors, and the treatment scenario.

Guidelines

Copiktra is included in several guidelines published by the National Comprehensive Cancer Network (NCCN).
- **CLL/SLL:** The NCCN guidelines for CLL/SLL (version 1.2021 – September 28, 2020) address CLL.[3] Copiktra is one of several therapies for relapsed or refractory therapy (category 2A). The

guidelines note that CLL and SLL are different manifestations of the same condition and are treated similarly.

- **Follicular Lymphoma:** The NCCN guidelines for B-cell Lymphomas (version 4.2020 – August 13, 2020) recommend Copiktra as second-line and subsequent therapy in patients with follicular lymphoma (Grade 1 to 2) among patients relapsed or refractory after two prior therapies (category 2A).[4]
- **Marginal Zone Lymphoma:** The NCCN guidelines for B-Cell Lymphomas (version 4.2020 – August 13, 2020) recommend Copiktra as second-line and subsequent therapy for marginal zone lymphomas that are refractory or refractory to two prior therapies.[4] Other regimens are recommended first-line including many that are rituximab-based. Many recommendations for the different types of gastric MALT and nongastric MALT lymphoma follow those of marginal zone lymphomas.

Safety

Copiktra has a Boxed Warning regarding fatal and serious toxicities such as infections, diarrhea or colitis, cutaneous reactions, and pneumonitis.[1] Copiktra was approved with a Risk Evaluation and Mitigation Strategy (REMS) program to assist physicians in the management of these risks. Other Warnings are present regarding hepatotoxicity, neutropenia, and embryofetal toxicity.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Copiktra. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Copiktra is recommended in those who meet the following criteria:

FDA-Approved Indications

46. Chronic Lymphocytic Leukemia (CLL). Approve for 3 years if the patient has tried two prior therapies.
Note: Examples of therapies include Imbruvica® (ibrutinib capsules and tablets); Venclexta® (venetoclax tablets) with or without rituximab; Venclexta plus Gazyva® (obinutuzumab injection for intravenous use); chlorambucil plus Gazyva; chlorambucil plus rituximab; FCR (fludarabine, cyclophosphamide, and rituximab); FR (fludarabine plus rituximab); PCR (pentostatin, cyclophosphamide, and rituximab); Treanda® (bendamustine injection) with or without rituximab; high-dose methylprednisolone (HDMP) plus rituximab; Campath® (alemtuzumab injection for intravenous use) with or without rituximab; Calquence® (acalabrutinib capsules); Zydelig® (idelalisib tablets) with or without rituximab; Gazyva; Rituxan; Arzerra® (ofatumumab injection for intravenous use); or chlorambucil.

47. Follicular Lymphoma. Approve for 3 years if the patient has tried two prior therapies.
Note: Examples of therapies include Treanda® (bendamustine injection) plus rituximab; Treanda plus Gazyva® (obinutuzumab injection for intravenous use); CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) plus Gazyyva; RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone); RCVP (rituximab, cyclophosphamide, vincristine, prednisone); chlorambucil with or without rixtuximab; cyclophosphamide with or without rituximab; Gazyva; Revlimid®

(lenalidomide capsules); CVP plus Gazyva; Zydelig® (idelalisib tablets); chlorambucil; cyclophosphamide; or Aliqopa® (copanlisib injection for intravenous use).

48. Small Lymphocytic Lymphoma (SLL). Approve for 3 years if the patient has tried two prior therapies.
Note: Examples of therapies include Imbruvica® (ibrutinib capsules and tablets); Venclexta® (venetoclax tablets) with or without rituximab; Venclexta plus Gazyva® (obinutuzumab injection for intravenous use); chlorambucil plus Gazyva® (obinutuzumab injection for intravenous use); chlorambucil plus rituximab; FCR (fludarabine, cyclophosphamide, and rituximab); FR (fludarabine plus rituximab); PCR (pentostatin, cyclophosphamide, and rituximab); Treanda® (bendamustine injection) with or without rituximab; high-dose methylprednisolone (HDMP) plus rituximab; Campath® (alemtuzumab injection for intravenous use) with or without rituximab; Calquence® (acalabrutinib capsules); Zydelig® (idelalisib tablets) with or without rituximab; Gazyva; Rituxan; Arzerra® (ofatumumab injection for intravenous use); or chlorambucil.

Other Uses with Supportive Evidence

200. MALT Lymphoma (Gastric and Nongastric). Approve for 3 years if the patient has tried two other therapies.
Note: Examples of therapies include rituximab; Treanda® (bendamustine injection for intravenous use) plus rituximab; RCHOP (rituximab, cyclophosphamide, vincristine, prednisone); RCVP (rituximab, cyclophosphamide, vincristine, prednisone); chlorambucil with or without rituximab; cyclophosphamide with or without rituximab; Imbruvica® (ibrutinib tablets and capsules); Zydelig® (idelalisib tablets); Revlimid® (lenalidomide capsules) with or without rituximab; or Aliqopa® (copanlisib injection for intravenous use).

201. Marginal Zone Lymphoma. Approve for 3 years if the patient has tried two other therapies.
Note: Examples of therapies include rituximab; Treanda® (bendamustine injection for intravenous use) plus rituximab; RCHOP (rituximab, cyclophosphamide, vincristine, prednisone); RCVP (rituximab, cyclophosphamide, vincristine, prednisone); chlorambucil with or without rituximab; cyclophosphamide with or without rituximab; Imbruvica® (ibrutinib tablets and capsules); Zydelig® (idelalisib tablets); Revlimid® (lenalidomide capsules) with or without rituximab; or Aliqopa® (copanlisib injection for intravenous use).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Copiktra is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

270. Copiktra® capsules [prescribing information]. Needham, MA: Verastem; July 2019.
271. Hallek M, Shanafelt TD, Eichhorst B. Chronic lymphocytic leukemia. *Lancet*. 2018;391:1524-1537.
272. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (Version 1.2021 – September 28, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 28, 2020.
273. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 4.2020 – August 13, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 28, 2020

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	Not applicable.	09/26/2018
Annual Revision	Alternatives are now listed as examples in the criteria in a note. Criteria were added for patients with marginal zone lymphoma and MALT lymphoma (gastric and nongastric).	10/09/2019
Annual Revision	No criteria changes.	11/04/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Cotellic Prior Authorization Policy
- Cotellic® (cobimetinib tablets – Genentech/Roche)

REVIEW DATE: 07/08/2020

OVERVIEW
Cotellic is a mitogen-activated extracellular signal regulated kinase (MEK) inhibitor indicated in combination with Zelboraf® (vemurafenib tablets), for the treatment of patients with unresectable or metastatic melanoma with the *BRAF V600E* or *V600K* mutation.[1]

Guidelines
NCCN guidelines for melanoma (version 3.2020 – May 18, 2020) recommend BRAF/MEK inhibitor combinations for first-line (preferred if clinically needed for early response) and subsequent treatment of metastatic or unresectable melanoma with a *V600* activating mutation.[2] While combination BRAF/MEK inhibition is preferred, if a combination is contraindicated, monotherapy with a BRAF inhibitor (Tafinlar® [dabrafenib capsules] or Zelboraf® [vemurafenib tablets]) is recommended option, particularly if the patient is not a candidate for checkpoint immunotherapy. Following resection of limited metastatic disease with a *BRAF V600*-activating mutation, BRAF/MEK combination therapy is among the treatment options for patients with no evidence of disease. Tafinlar + Mekinist® (trametinib tablets) is also recommended in guidelines as adjuvant therapy (including for nodal recurrence) in some patients with Stage III disease, including use post-surgery or use after complete lymph node dissection. If unacceptable toxicity to Tafinlar/Mekinist, other BRAF/MEK combinations can be considered.

POLICY STATEMENT
Prior authorization is recommended for prescription benefit coverage of Cotellic. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Cotellic is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Melanoma.** Approve Cotellic for 3 years if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient has unresectable, advanced, or metastatic melanoma; AND
   - **B)** Patient has *BRAF V600* mutation-positive disease; AND
   - **C)** Cotellic is being prescribed in combination with Zelboraf (vemurafenib tablets).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cotellic is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

265. Cotellic tablets [prescribing information]. South San Francisco, CA: Genentech USA Inc./Roche; January 2018.
266. The NCCN Melanoma Clinical Practice Guidelines in Oncology (Version 3.2020 – May 18, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 2, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early annual revision	Remove continuation criteria in melanoma; now all approvals require that the Cotellic is taken in combination with Zelboraf AND that the patient has unresectable, advanced, or metastatic melanoma with a BRAF mutation.	05/23/2018
Annual revision	No criteria changes.	06/18/2019
Annual revision	No criteria changes.	07/08/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Daurismo Prior Authorization Policy

- Daurismo™ (glasdegib tablets – Pfizer)

REVIEW DATE: 12/02/2020

OVERVIEW

Daurismo, a hedgehog pathway inhibitor, is indicated, in combination with low-dose cytarabine, for the treatment of newly-diagnosed **acute myeloid leukemia** (AML) in adults who are ≥ 75 years of age or who have comorbidities that preclude use of intensive induction chemotherapy.[1]

Disease Overview

AML is a heterogeneous hematologic malignancy that is hallmarked by clonal expansion of myeloid blasts in the peripheral blood, bone marrow, and/or other tissues.[2] It is a rather common form of acute leukemia in adults and it has the largest number of annual deaths from leukemias in the US. Around 19,940 people will be diagnosed with AML in 2020, and 11,180 patients will die from the condition. The median age at diagnosis is 66 years of age. Over one-half and approximately one-third of patients receive the diagnosis at ≥ 65 and ≥ 75 years of age, respectively. The incidence of AML, along with myelodysplastic syndrome (MDS) is rising as patients become older. Environmental factors play a role and include prolonged exposure to petrochemicals; solvents such as benzene; pesticides; and ionizing radiation. Also, two cytotoxic agents that are associated with therapy-related MDS/AML are alkylating agents (e.g., cyclophosphamide) and topoisomerase inhibitors (e.g., doxorubicin). Antimetabolite therapy, notably fludarabine, has also been associated with MDS/AML in patients with lymphoproliferative disorders, especially when given in combination with alkylating agents. Molecular or karyotypic abnormalities can also be identified. Treatment of AML can involve the following modalities at various stages: chemotherapy, radiation therapy, chemotherapy with stem cell transplant, and other drug therapy.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines address Daurismo.[2]

- **Acute Myeloid Leukemia:** NCCN guidelines for AML (version 2.2021 – November 12, 2020) recommended Daurismo with low-dose cytarabine for patients ≥ 60 years of age who are not

candidates for intensive remission induction therapy or declines without an actionable mutation (category 2A). Daurismo is also recommended with low-dose cytarabine as post-induction therapy for patients ≥ 60 years of age who had a response to previous low-intensity therapy. (category 2A).

Safety

Daurismo has a Boxed Warning regarding embryofetal toxicity.[1] Also, patients receiving Daurismo may develop QTc prolongation and ventricular arrhythmias. Serious adverse reactions were reported in 79% of patients given Daurismo plus low-dose cytarabine and the most common were febrile neutropenia (29%), pneumonia (23%), hemorrhage (12%), anemia (7%), and sepsis (7%). Consider specific drug-drug interactions among patients given Daurismo (e.g., strong cytochrome P450 [CYP]3A4 inhibitors, strong CYP3A4 inducers, QTc prolonging medications).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Daurismo. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Daurismo is recommended in those who meet the following criteria:

FDA-Approved Indication

136. Acute Myeloid Leukemia (AML). Approve for 3 years if the patient meets the following criteria (A and B):
- **A)** Patient is using the medication in combination with cytarabine; AND
- **B)** Patient must meet one of the following criteria (i or ii):
  - **i.** Patient is using the medication for treatment induction and meets one of the following (a or b):
    - **a)** Patient is ≥ 75 years of age; OR
    - **b)** Patient meets both of the following [(1) and (2)]:
      1. Patient is ≥ 18 years of age; AND
      2. According to the prescriber, the patient has comorbidities that precludes the use of intensive induction chemotherapy; OR
  - **ii.** Patient meets both of the following (a and b):
    - **a)** Patient is ≥ 18 years of age; AND
    - **b)** Patient is continuing the medication as post-induction therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Daurismo is not recommended in the following situations:

147. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

466. Daurismo™ tablets [prescribing information]. New York, NY: Pfizer; November 2018.
467. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (Version 2.2021 – November 12, 2020). © 2010 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 4, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	Not applicable.	11/28/2018
Selected Revision	For the criteria that requires that the patient is: 1) ≥ 75 years of age or 2) according to the prescribing physician, the patient has comorbidities that preclude the use of intensive induction chemotherapy, it was clarified that this applies to use in treatment induction. Added approval for Daurismo in patients with acute myeloid leukemia who are continuing the agent with cytarabine for post-remission therapy.	02/06/2019
Annual Revision	The word "prescriber" replace the section in the criteria that previously stated "prescribing physician". Also, per National Comprehensive Cancer Network guidelines for acute myeloid leukemia, the criteria that allowed continuation of Daurismo as post-remission therapy was changed to "post-induction" therapy.	12/11/2019
Annual Revision	**Acute Myeloid Leukemia:** For criteria regarding induction therapy, the age qualifier of ≥ 18 years was added to the criteria which states "according to the prescriber, the patient has comorbidities that preclude the use of intensive induction chemotherapy." For post-induction therapy, the age qualifier that the patient is ≥ 18 years of age was also added.	12/02/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Erivedge Prior Authorization Policy

- Erivedge® (vismodegib capsules – Genentech)

REVIEW DATE: 11/04/2020

OVERVIEW

Erivedge, an inhibitor of the hedgehog signaling pathway, is indicated for the treatment of adults with metastatic **basal cell carcinoma**, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.[1] It binds to and inhibits Smoothened, a transmembrane protein involved in Hedgehog signal transduction.

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines for basal cell carcinoma (version 1.2020 – October 24, 2019) note that surgical approaches offer the most effective and efficient means for accomplishing a cure; radiation therapy may be chosen as the primary treatment in order to achieve optimal overall results.[2] For residual disease when surgery and radiation therapy are contraindicated and for recurrent disease with nodal or distant metastases, a hedgehog pathway inhibitor should be considered.

For central nervous system cancers, NCCN guidelines (version 3.2019 – September 11, 2020) list Erivedge as a treatment option for ceratin patients with recurrent disease, if chemotherapy has been tried and if there is a mutation of the sonic hedgehog pathway.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Erivedge. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Erivedge is recommended in those who meet the following criteria:

FDA-Approved Indications

49. Basal Cell Carcinoma, Metastatic. Approve for 3 years.

50. Basal Cell Carcinoma, Locally Advanced. Approve for 3 years if the patients meets ONE of the following conditions (A or B):

~~82.~~ Initial Therapy. Approve if the patient meets ONE of the following (i or ii):

i. Patient has recurrent basal cell carcinoma following surgery or radiation therapy; OR

ii. Patient meets BOTH of the following (a and b):

a) Patient is not a candidate for surgery; AND

~~a.~~ According to the prescriber, the patient is not a candidate for radiation therapy.

83. Patient is Currently Receiving Erivedge. Approve.

Other Uses with Supportive Evidence

51. Central Nervous System Cancer. (Note: This includes brain and spinal cord tumors.) Approve for 3 years if the patient meets BOTH of the following (A and B):
- **A)** Patient has tried at least one chemotherapy agent; AND
  Note: Examples of chemotherapy include etoposide, carboplatin, cisplatin.
- **B)** According to the prescriber, the patient has a mutation of the sonic hedgehog pathway.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Erivedge is not recommended in the following situations:

202. Basal Cell Carcinoma (Locally Advanced or Metastatic), in Patients with Disease Progression While on Odomzo® (sonidegib capsules). [Note: This does not apply to patients already started on Erivedge. Refer to criteria for basal cell carcinoma, Locally Advanced for Patients Currently Receiving Erivedge.] There are no data to support the use of Erivedge in patients who have experienced disease progression on Odomzo. Previous use of a hedgehog inhibitor was not allowed in the pivotal study for Odomzo.[3] Patients who develop resistance to one of the hedgehog pathway inhibitors are not expected to respond to another hedgehog pathway inhibitor. There is an open-label study which evaluated patients (n = 9) with advanced basal cell carcinoma who had progressed on Erivedge that showed resistance to Odomzo, another hedgehog signaling pathway used in basal cell carcinoma.[7]

203. Metastatic Colorectal Cancer. Erivedge is not recognized in the treatment recommendations for colon cancer from the NCCN (version 4.2020 – June 15, 2020).[4] In combination with standard of care treatment for first-line disease, Erivedge did not confer incremental clinical benefit as measured by progression-free survival (PFS) compared with standard care therapy alone. A Phase II study was designed to assess whether Erivedge would prolong PFS when combined with standard of care therapy (FOLFOX [leucovorin, fluorouracil, oxaliplatin] or FOLFIRI [leucovorin, fluorouracil, irinotecan] in combination with Avastin® [bevacizumab injection]) in patients requiring first-line treatment for metastatic colorectal cancer.[3] Adults with histologically confirmed disease were randomized 1:1 to Erivedge or placebo (n = 199). There was not a significant difference is median PFS or 12-month survival with Erivedge vs. placebo.

204. Ovarian Cancer. The NCCN guidelines for Ovarian Cancer (version 1.2020 – March 11, 2020) do not address the use of Erivedge for the management of ovarian cancer.[6] The prespecified magnitude of PFS was not achieved in a Phase II, randomized, double-blind, placebo-controlled trial in adults with histologically confirmed epithelial ovarian carcinoma, primary peritoneal carcinoma, or fallopian tube carcinoma. The study was conducted to determine an estimate of clinical benefit of maintenance therapy with Erivedge in the setting of second or third complete remission as measured by PFS using radiographic assessment.[5] Eligible patients had received chemotherapy (platinum based and/or non-platinum based) for recurrent disease and had achieved complete response after their most recent chemotherapy regimen. PFS was not statistically different with Erivedge vs. placebo.

205. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

274. Erivedge® capsules [prescribing information]. South San Francisco, CA: Genentech USA, Inc.; July 2020.
275. The NCCN Basal Cell Skin Cancer Clinical Practice Guidelines in Oncology (Version 1.2020 – October 24, 2019). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 28, 2020.

276. Berlin JD, Bendell JC, Hart LL, et al. A randomized phase II trial of vismodegib versus placebo with FOLFOX or FOLFIRI and bevacizumab in patients with previously untreated metastatic colorectal cancer. *Clin Cancer Res*. 2013;19(1):258-267.
277. NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 4.2020 – June 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 28, 2020.
278. Kaye SB, Fehrenbacher L, Holloway R, et al. A Phase II, randomized, placebo-controlled study of vismodegib as maintenance therapy in patients with ovarian cancer in second or third complete remission. *Clin Cancer Res*. 2012;18(23):6509-6518.
279. NCCN Ovarian Cancer Clinical Practice Guidelines in Oncology (Version 1.2020 – March 11, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 28, 2020.
280. Danial C, Sarin KY, Oro AE, Chang AL. An investigator-initiated open-label trial of sonidegib in advanced basal cell carcinoma patients resistant to vismodegib. *Clin Cancer Res*. 2016;22(6):1325-1329.
281. NCCN Central Nervous System Cancer Clinical Practice Guidelines in Oncology (Version 3.2020 – September 11, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 28, 2020.

HISTORY

Type of Revision	Summary of Changes*	Review Date
Annual Revision	**Patients Already Started on Erivedge:** This criterion only applies to basal cell carcinoma, locally advanced disease; reformat to address in the criteria section for this condition.	10/10/2018
Annual Revision	**Central Nervous System Cancers:** To align with NCCN guidelines, approve for 3 years if the patient has tried chemotherapy, and if, according to the prescriber, there is a mutation of the sonic hedgehog pathway.	10/16/2019
Annual Revision	**Basal Cell Carcinoma, Locally Advanced:** For the criterion applying to a patient who is not a candidate for radiation therapy, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician).	11/04/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Erleada (apalutamide tablets – Janssen Pharmaceuticals)

DATE REVIEWED: 03/04/2020

OVERVIEW

Erleada is indicated for the treatment of patients with non-metastatic, castration-resistant prostate cancer (nmCRPC).[1] It is also indicated in patients with metastatic castration-sensitive prostate cancer (CSPC). Patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or the patient should have had a bilateral orchiectomy. Erleada is an androgen receptor inhibitor that binds directly to the ligand-binding domain of the androgen receptor.

GUIDELINES

According to the National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer, (version 4.2019 – August 19, 2019) for nmCRPC, androgen deprivation therapy (ADT) is continued to maintain castrate serum levels of testosterone (< 50 ng/dL).[2] Erleada, Xtandi® (enzalutamide capsules), and Nubeqa® (darolutamide tablets) are all category 1 recommended options especially if the PSADT is ≤ 10 months. Other secondary hormone therapy is recommended if PSADT is ≤ 10 months (category 2A): for non-metastatic (M0) CRPC, the options are nilutamide, flutamide, bicalutamide, ketoconazole, corticosteroids. For metastatic, castration-naïve disease, ADT in combination with abirateron + prednisone, Erleada, and Xtandi are all category 1 recommended options. Yonsa (abiraterone acetate) with methylprednisolone is a category 2B recommendation.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Erleada. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Erleada is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Prostate Cancer – Non-Metastatic, Castration-Resistant.** Approve Erleada for 3 years if the patient meets one of the following criteria (A or B):
   - **A)** The medication is used in combination with a gonadotropin-releasing hormone (GnRH) analog. Note: Examples are Lupron (leuprolide acetate for injection), Lupron Depot (leuprolide acetate for depot suspension), Trelstar (triptorelin pamoate for injectable suspension), Zoladex (goserelin acetate implant), Vantas (histrelin acetate subcutaneous implant), Firmagon (degarelix for injection); OR
   - **B)** The patient has had a bilateral orchiectomy.
2. **Prostate Cancer – Metastatic, Castration-Sensitive.** Approve for 3 years if the patient meets one of the following criteria (A or B):
   - **A)** The medication is used in combination with a gonadotropin-releasing hormone (GnRH) analog. Note: Examples are Lupron (leuprolide acetate for injection), Lupron Depot (leuprolide acetate for depot suspension), Trelstar (triptorelin pamoate for injectable suspension), Zoladex (goserelin acetate implant), Vantas (histrelin acetate subcutaneous implant), Firmagon (degarelix for injection); OR
   - **B)** The patient has had a bilateral orchiectomy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Erleada has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

206. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

241. Erleada™ [prescribing information]. Horsham, PA: Janssen Pharmaceutical Companies; September 2019.
242. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (Version 4.2019 – August 19, 2019). © 2019 National Comprehensive Cancer Network Inc. Available at: http://www.nccn.org. Accessed February 25, 2020.

HISTORY

Type of Revision	Summary of Changes*	Date Reviewed
New Policy	New criteria	02/16/2018
Annual revision	No criteria changes	02/27/2019
Selected revision	Added new FDA-approved indication for metastatic castration-sensitive prostate cancer. Also added criteria for both indications that the medication is used in combination with gonadotropin-releasing hormone agonist or patient has had an orchiectomy.	09/25/2019

Annual revision	For concomitant therapy with gonadotropin-releasing hormone agonist changed verbiage from "agonist" to "analog" since antagonist can also be used. Added Firmagon as example for both conditions.	03/04/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Erlotinib Prior Authorization Policy
- Erlotinib (Tarceva® tablets – Genentech/Astellas/OSI Pharmaceuticals; generics)

REVIEW DATE: 03/17/2021

OVERVIEW

Erlotinib, a kinase inhibitor, is indicated for the following uses:[1]

- **Non-Small Cell Lung Cancer**, treatment of tumors with epidermal growth factor receptor **(EGFR) exon 19 deletions** or **exon 21 (L858R) substitution mutations** as detected by an FDA-approved test receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen. The safety and efficacy of erlotinib have not been established in patients with NSCLC whose tumors have other EGFR mutations.
- **Pancreatic Cancer**, first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer, in combination with gemcitabine.

Guidelines

- **Non-Small Cell Lung Cancer:** The National Comprehensive Cancer Network (NCCN) guidelines for NSCLC (version 4.2021 – March 3, 2021) recommend *EGFR* mutation testing in patients with nonsquamous NSCLC (i.e., adenocarcinoma, large cell) or in NSCLC not otherwise specified (NOS).[2] Erlotinib, Iressa® (gefitinib tablets), Gilotrif™ (afatinib tablets) Vizimpro® (dacomitinib tablets), and Tagrisso™ (osimertinib tablets) [preferred] are all category 1 recommended for the first-line treatment in patients with sensitizing *EGFR*-mutation positive NSCLC discovered before first-line chemotherapy. Erlotinib + Cyramza (ramucirumab injection) and erlotinib + bevacizumab are both category 2A recommended options.
- **Pancreatic Cancer:** NCCN guidelines for pancreatic adenocarcinoma (version 2.2021 – February 25, 2021) recommend erlotinib and gemcitabine combination for systemic therapy in patients with locally advanced unresectable disease with good performance status (category 2A).[4] Gemcitabine + erlotinib is also recommended for metastatic disease in this population (category 1).
- **Bone Cancer:** The NCCN bone cancer guidelines (version 1.2021 – November 20, 2020) list single-agent erlotinib as one of the systemic treatment options for patients with recurrent chordoma.[6] Other systemic therapy options include imatinib with or without cisplatin or sirolimus, Sutent® (sunitinib capsules), Tykerb® (lapatinib tablets) [for patients with EGFR-positive disease], or Nexavar® (sorafenib tablets).
- **Renal Cell Carcinoma:** The NCCN guidelines for Kidney Cancer (version 2.2021 – February 3, 2021) recommend erlotinib as one of the first-line therapies for relapse or surgically unresectable Stage IV disease with non-clear cell histology (category 2A).[5] Erlotinib, either as monotherapy or in combination with bevacizumab (combination therapy for selected patients with advanced papillary RCC), are category 2A recommended options.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of erlotinib. All approvals are provided for 3 years in duration as noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of erlotinib is recommended in those who meet the following criteria:

FDA-Approved Indications

52. Non-Small Cell Lung Cancer (NSCLC). Approve for 3 years if the patient meets the following criteria (A and B):
~~1.~~Patient has metastatic epidermal growth factor receptor (EGFR) mutation-positive disease; AND
~~2.~~Patient meets ONE of the following criteria (i or ii):
- **i.** Patient has epidermal growth factor receptor (EGFR) exon 19 deletions as detected by an approved test; OR
- **ii.** Patient has exon 21 (L858R) substitution mutations as detected by an approved test.

53. Pancreatic Cancer. Approve for 3 years if the medication is used in combination with gemcitabine.

Other Uses with Supportive Evidence

3. Bone Cancer. Approve for 3 years in patients who meet the following criteria (A and B):
A) Patient has chordoma; AND
B) Patient has tried at least one previous therapy.

4. Renal Cell Carcinoma (RCC). Approve for 3 years if the patient has relapsed or Stage IV non-clear cell histology RCC.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of erlotinib is not recommended in the following situations:

207. Biliary Cancer. There were no differences in PFS and OS between gemcitabine/oxaliplatin and gemcitabine/oxaliplatin with the addition of erlotinib in patients with metastatic biliary-tract cancer (cholangiocarcinoma, gallbladder cancer, or ampulla of Vater cancer) in one Phase III, open-label, randomized study (n = 268); however, in a subgroup of patients with cholangiocarcinoma, the addition of erlotinib to chemotherapy resulted in a significantly prolonged PFS (5.9 months vs. 3.0 months; P = 0.049).[7,8] In patients with advanced (unresectable or metastatic) cholangiocarcinoma or gallbladder cancer, combination therapy with bevacizumab and erlotinib showed clinical activity in one Phase II study (n = 56).[9] Among six patients with confirmed PRs, the median duration of response was 8.4 months (95% CI: 6.0, 11.7). Eighty-seven percent of patients progressed with a median time to disease progression of 4.4 months (95% CI: 3.0, 7.8). Median OS was 9.9 months (95% CI: 7.2, 13.6). As single-agent therapy in one Phase II study, erlotinib showed benefit in patients with unresectable or metastatic biliary cancer previously treated with not more than one prior systemic or locoregional therapy (n = 42).[10] In all, 17% (n = 1/7) of patients (95% CI: 7% to 31%) were progression free at 6 months. One Phase II trial evaluated the efficacy of erlotinib and docetaxel in patients with refractory (up to two prior systemic therapies) hepatocellular (n = 14) and biliary (n = 11) cancers.[11] The 16-week PFS rate was 64% for biliary tract cancer (95% CI: 29.7, 84.5), meeting the 16-week PFS endpoint of ≥ 30%. Median OS was 5.7 months and similar to historical data with single-agent erlotinib therapy.

2. Breast Cancer. One Phase II, non-randomized, open-label, bi-institutional trial did not support beneficial effect of erlotinib plus bevacizumab in patients with metastatic breast cancer with stage IV disease that was stable or had progressed after treatment with one or two chemotherapy regimens; if

the patient's tumor was human epidermal growth factor receptor-2 (HER-2) positive, prior therapy with trastuzumab was required (n = 38).[12] As single-agent therapy, erlotinib had minimal activity in unselected, previously treated women with locally advanced or metastatic breast cancer in one multicenter, Phase II study (n = 69).[13] Metronomic (frequent low-dose) capecitabine tablets and cyclophosphamide plus Bevacizumab and erlotinib was effective in patients with untreated advanced metastatic HER-2 negative, estrogen receptor-negative, and progesterone receptor-poor advanced breast cancer (n = 26).[14] Among 24 patients assessable for response, 4% of patients has a CR [n = 1], 58% of patients had PR (n = 14), 21% of patients had stable disease (SD) > 9 weeks duration (n = 5) and 4% of patients (n = 1) had early progression of disease. The overall clinical benefit (CR + PR + SD > 24 weeks) was 75% (95% CI: 53, 90). Median time to progression was 43 weeks (95% CI: 21, 69). OS was 108 months (95% CI: 70, 110).

3. **Colorectal Cancer, Metastatic (mCRC).** In Phase II studies in patients with untreated mCRC, efficacy has not been demonstrated.[15-18] In one Phase III trial, patients with mCRC received doublet chemotherapy plus bevacizumab as initial therapy.[19] Patients without tumor progression were randomized to maintenance therapy with bevacizumab plus erlotinib (n = 80) or bevacizumab alone (n = 79). Median PFS was 5.7 months with the combination and 4.2 months with bevacizumab alone (HR 0.79; 95% CI: 0.55, 1.12; P = 0.19). The rate of any Grade 3/4 toxicity was 53% with bevacizumab/erlotinib vs. 13% with bevacizumab alone. Another Phase III trial, OPTIMOX3, assessed the efficacy of maintenance bevacizumab plus erlotinib therapy (n = 224) after induction chemotherapy compared with bevacizumab alone (n = 228) in patients with unresectable metastatic colorectal cancer.[20] The median PFS from maintenance was 5.4 months in the bevacizumab plus erlotinib group compared with 4.9 months in the bevacizumab group (HR 0.81; 95% CI: 0.66, 1.01; P = 0.059). The median OS from maintenance was 24.9 months compared with 22.1 months for bevacizumab plus erlotinib and bevacizumab alone, respectively. The Phase III Nordic ACT2 trial demonstrated that the addition of erlotinib to bevacizumab as maintenance therapy in patients with KRAS wild-type mCRC did not significantly improve PFS or OS.[21]

4. **Glioblastoma Multiforme (GBM).** In one Phase II study, concurrent radiation therapy (RT) and temozolomide in combination with erlotinib in patients newly diagnosed with glioblastoma (n = 27) was not efficacious.[22] In two Phase II studies, erlotinib plus temozolomide given during and after RT produced favorable median survival, and PFS, as well as 12- or 14-month survival rates in patients with newly diagnosed GBM or gliosarcoma.[23,24] In patients with newly diagnosed (untreated; could have had resection) GBM or gliosarcoma who received erlotinib plus temozolomide during and after radiation, median survival was longer with erlotinib plus temozolomide vs. historical controls (19.3 months vs. 14.1 months, respectively; HR for survival 0.64; 95% CI: 0.45, 0.91; P = 0.01) in one open-label, single-center, Phase II trial (n = 65).[23] The historical controls were comparable patients from two prospective, Phase II trials (n = 128); the first trial included the use of Thalomid (thalidomide capsules) in combination with temozolomide during and after radiotherapy; the second that included the use of *cis*-retinoic acid with temozolomide during and after radiotherapy. In one open-label, Phase I/II trial, treatment with erlotinib plus temozolomide during and after RT resulted in favorable survival rate (61% of patients were alive at 1 year) and median PFS (7.2 months) in patients with newly diagnosed GBM (following resection); however, there was no significant difference in OS with the addition of erlotinib compared with the temozolomide/RT arm of a historical control trial (15.3 months vs. 15 months, respectively).[24] Erlotinib has failed to demonstrate benefit in recurrent glioblastomas.[25-28]

5. **Head and Neck Cancer, Squamous Cell, Recurrent and/or Metastatic.** Two Phase II studies assessed the use of erlotinib and bevacizumab in different settings and showed promising results.[29,30] One multicenter, Phase II trial assessed the addition of bevacizumab and erlotinib to chemoradiation as first-line treatment for previously untreated patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) [n = 60].[29] After a median follow-up of 32 months the estimated 3-year

PFS and OS rates were 71% and 82%, respectively. After induction therapy, 65% of patients had major responses; after completion of therapy 95% of patients had either partial or complete radiographic responses. One multi-institutional Phase I/II study enrolled patients with recurrent or metastatic SCCHN (previously treated with ≤ 1 prior regimen for recurrent disease) to receive erlotinib and bevacizumab (n = 56).[30] The median OS and PFS durations were 7.1 months (95% CI: 5.7, 9.0) and 4.1 months (95% CI: 2.8, 4.4), respectively. Treatment with erlotinib monotherapy produced few PRs in unselected (EGFR status not known at baseline) patients with locally recurrent and/or metastatic SCCHN in one open-label, Phase II clinical trial (n = 115); 38.3% of patients achieved SD for a median of 16.1 weeks.[31] In one Phase II study, 204 patients with locally advanced SCCHN were randomized to receive cisplatin in combination with RT with or without erlotinib.[32] Complete response rates evaluated by central review were reported in 40% of patients (n = 42/105) on cisplatin/RT vs. 52% of patients (n = 51/99) on cisplatin/RT/erlotinib (P = 0.08). At a median follow-up of 26 months and 54 progression events, there was no difference in PFS between the two treatment arms (HR 0.0; P = 0.71). In a Phase II study, patients with recurrent SCCHN were treated with erlotinib for 12 months (n = 31). The OS was 61% at 1 year and 56% at 2 years.[33] Disease-free survival was 54% at 1 year and 45% at 2 years. The mean time to recurrence (n = 16) was 8.7 months. Only 8 patients completed the full 12-month course of erlotinib; the median duration of erlotinib therapy was 5 months.

6. **Hepatocellular Carcinoma (HCC), Advanced.** Some Phase II studies have reported activity of erlotinib in patients with HCC while others have not.[34-36] In one Phase III trial, patients with advanced HCC were randomized to Nexavar/erlotinib (n = 362) or Nexavar/placebo (n = 358).[37] Median OS, the primary endpoint, was similar in both groups: 9.5 vs. 8.5 months for Nexavar/erlotinib and Nexavar/placebo, respectively (HR 0.929; P = 0.408). A network meta-analysis of 11 randomized controlled trials with 6,594 patients with advanced hepatocellular carcinoma concluded that Nexavar in combination with erlotinib demonstrated better short-term and long-term efficacy compared with other drugs.[38]

7. **Occult Primary/Cancer of Unknown Primary Site (CUP).** The combination of bevacizumab and erlotinib (alone or combined with paclitaxel and carboplatin) had activity as first- or second-line therapy in patients with occult primary tumors (adenocarcinoma, poorly differentiated carcinoma, poorly differentiated adenocarcinoma, poorly differentiated squamous carcinoma).[39]

8. **Renal Cell Carcinoma (RCC), Advanced – Clear Cell Histology.** Efficacy with erlotinib has not been demonstrated in patients with clear cell histology.[5]

9. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Tarceva® tablets [prescribing information]. South San Francisco, CA: Genentech; October 2016.
2. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 4.2021 – March 3, 2021) © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed March 18, 2021.
3. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 3.2019 – October 18, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed March 9, 2020.
4. The NCCN Pancreatic Adenocarcinoma Clinical Practice Guidelines in Oncology (version 2.2021 – February 25, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed March 18, 2021.
5. The NCCN Kidney Cancer Clinical Practice Guidelines in Oncology (version 2.2021 – February 3, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed March 15, 2021.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes	03/13/2019
Annual Revision	Added generic tablets to drug targets and changed to generic policy name. For "Bone Cancer – Chordoma", deleted reference to "recurrent disease" and changed criteria to state patients "who have tried at least one previous therapy."	03/11/2020
Annual Revision	**Non-Small Cell Lung Cancer:** Moved "Epidermal Growth Factor Receptor (EGFR) Mutation-Positive" descriptor from indication heading to criteria. **Pancreatic Cancer:** Deleted "Locally Advanced, Unresectable, or Metastatic" from indication heading since it is not needed. Changed wording from erlotinib is "prescribed" in combination with gemcitabine to "the medication is used" in combination with gemcitabine, in-line with other policies. **Renal Cell Carcinoma (RCC):** Deleted "Advanced – Non-Clear Cell Histology" from indication. Within criteria added to approve "if the patient has relapsed or Stage IV non-clear cell histology RCC". **Bone Cancer:** Deleted "Chordoma" from indication descriptor and added it as criteria.	03/17/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Farydak® (panobinostat capsules – Novartis Pharmaceuticals)

DATE REVIEWED: 04/22/2020

OVERVIEW

Farydak is a histone deacetylase (HDAC) inhibitor, which, in combination with Velcade® (bortezomib injection) and dexamethasone, is indicated for the treatment of patients with multiple myeloma who have received at least two prior regimens, including Velcade and an immunomodulatory drug (IMiD) [i.e., Thalomid® {thalidomide capsules}, Revlimid® {lenalidomide capsules}, Pomalyst® {pomalidomide capsules}).[1] The recommended starting dose of Farydak is 20 mg, taken orally once every other day (QOD) for three doses per week in Weeks 1 and 2 of each 21-day cycle for up to eight cycles. Treatment may be continued for an additional eight cycles in patients with clinical benefit who do not experience unresolved severe or medically significant toxicity, up to a maximum of 16 cycles (48 weeks).

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines, which address diagnosis, treatment, and follow-up for patients with multiple myeloma (version 3.2020 – March 10, 2020), note that Farydak/Velcade/dexamethasone (category 1) is an Other Regimen for patients who have tried at least

two previous therapies, including Velcade and an IMiD, for treatment of previously treated disease.[2] Although not approved combinations, Farydak/Kyprolis® (carfilzomib injection) and Farydak/Revlimid/dexamethasone are also listed as potential Other Regimens for previously treated multiple myeloma (both category 2A). While there are small studies evaluating these combinations in previously treated multiple myeloma, there are multiple other regimens that NCCN classifies as Preferred Regimens for previously treated multiple myeloma. These regimens have a more established place in therapy and a stronger recommendation by NCCN.

Safety

There is a Farydak Risk Evaluation and Mitigation Strategy (REMS) program which consists of a communication plan to inform healthcare professionals of risks of cardiotoxicity and diarrhea and how to minimize these events.[3]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Farydak. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indications

54. Multiple Myeloma. Approve for 1 year if the patient meets the following conditions (A and B):
- **3.** Farydak will be taken in combination with Velcade® (bortezomib injection) and dexamethasone; AND
- **4.** The patient has previously tried Velcade and one immunomodulatory drug (i.e., Thalomid [thalidomide capsules], Revlimid [lenalidomide capsules], or Pomalyst [pomalidomide capsules]).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Farydak has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

208. Pancreatic Cancer. A Phase II study evaluating Farydak + Velcade in patients with pancreatic cancer who were progressing on gemcitabine-based therapy was discontinued early due to toxicity and a lack of response.[4]

209. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

282. Farydak® capsules [prescribing information]. East Hanover, NJ: Novartis; June 2016.
283. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (Version 3.2020 – March 10, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on April 20, 2020.
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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual revision	No changes to the criteria.	04/04/2018
Annual revision	No changes to the criteria.	04/10/2019
Annual revision	No changes to the criteria.	04/22/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Gavreto Prior Authorization Policy
- Gavreto™ (pralsetinib capsules – Blueprint Medicines Corporation)

REVIEW DATE: 09/09/2020; selected revision 12/09/2020

OVERVIEW

Gavreto, a kinase inhibitor, is indicated for the treatment of the following conditions:[1]

- **Medullary thyroid cancer**, in adult and pediatric patients ≥ 12 years of age with advanced or metastatic *RET*-mutant disease, who require systemic therapy.
- **Non-small cell lung cancer (NSCLC)**, in adult patients with metastatic rearranged during transfection (*RET*) fusion-positive disease as detected by an FDA approved test.
- **Thyroid cancer**, in adult and pediatric patients ≥ 12 years of age with advanced or metastatic *RET* fusion-positive disease who require systemic therapy and who are radioactive iodine-refractory.

  All of the above indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Guidelines

The National Comprehensive Cancer Network (NCCN) NSCLC guidelines (version 8.2020 – September 15, 2020) recommend Gavreto and Retevmo™ (selpercatinib capsules) as "preferred" (both category 2A) first-line therapies for RET rearrangement-positive disease.[2] For patients who were started on other systemic therapy options and had disease progression, Gavreto and Retevmo are recommended as "preferred" subsequent therapies.

Gavreto is not addressed in the thyroid guidelines. In the NCCN thyroid carcinoma guidelines (version 2.2020 – July 15, 2020) the use of Retevmo™ (selpercatinib capsules) is addressed in a variety of therapy settings.[3] Retevmo is a category 2A recommended therapy for patients with *RET* fusion-positive thyroid tumors that are radioactive iodine refractory. For recurrent, persistent, or metastatic medullary thyroid cancer, Caprelsa or Cometriq are both category 1 "preferred" options. Retevmo is listed as a category 2A "preferred" regimen for *RET* mutation-positive medullary thyroid cancer. For anaplastic carcinoma, molecular testing for actionable mutations is recommended; if positive for *RET* fusion, Retevmo can be considered (category 2A).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Gavreto. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Gavreto is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Medullary Thyroid Cancer.** Approve for 3 years if the patient meets the following criteria (A, B, and C):
   Note: For other types of thyroid cancer see criteria below for "Thyroid Cancer".
   A) Patient is ≥ 12 years of age; AND
   B) Patient has advanced or metastatic rearranged during transfection (*RET*)-mutant disease; AND
   C) The disease requires treatment with systemic therapy.

2. **Non-Small Cell Lung Cancer.** Approve for 3 years if the patient meets the following criteria (A, B, and C):
   C) Patient is ≥ 18 years of age; AND
   D) Patient has metastatic disease; AND
   E) Patient has rearranged during transfection (*RET*) fusion-positive disease as detected by an approved test.

3. **Thyroid Cancer.** Approve for 3 years if the patient meets the following criteria (A, B, C, and D):
   Note: For "Medullary Thyroid Cancer" see above criteria.

A) Patient is ≥ 12 years of age; AND
B) Patient has advanced or metastatic rearranged during transfection (RET) fusion-positive disease; AND
C) The disease is radioactive iodine-refractory; AND
D) The disease requires treatment with systemic therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Gavreto is not recommended in the following situations:

148. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

468. Gavreto capsules [prescribing information]. Cambridge, MA: Blueprint Medicines Corporation; December, 2020.
469. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 8.2020 – September 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed September 18, 2020.
470. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (version 2.2020 – July 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 7, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	09/09/2020
Selected Revision	**Non-Small Cell Lung Cancer:** Changed approval duration to 3 years from 1 year. Deleted "FDA-approved" in reference to testing and also deleted criteria requiring specialist physician, to be in-line with other oral oncology policies.	09/23/2020
Selected Revision	**Medullary Thyroid Cancer:** Added new approval condition and criteria based on FDA-approved indication. **Thyroid Cancer:** Added new approval condition and criteria based on FDA-approval.	12/09/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Gilotrif Prior Authorization Policy
- Gilotrif™ (afatinib tablets – Boehringer Ingelheim)

REVIEW DATE: 12/16/2020

OVERVIEW

Gilotrif is a tyrosine kinase inhibitor (TKI) indicated for the following:
- **Non-small cell lung cancer (NSCLC)**, first-line treatment of patients with metastatic disease whose tumors have non-resistant epidermal growth factor receptor (EGFR) mutations as detected by a FDA-approved test.[1] The safety and efficacy of Gilotrif have not been established in patients whose tumors have resistant *EGFR* mutations.
- **NSCLC, squamous,** for the treatment of patients with metastatic disease progressing after platinum-based chemotherapy.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for NSCLC (version 1.2021 – November 25, 2020) recommend Tarceva® (erlotinib tablets), Iressa® (gefitinib tablets), Gilotrif, Vizimpro® (dacomitinib tablets), and Tagrisso™ (osimertinib tablets) as Category 1 recommended options for the first-line treatment in patients with sensitizing *EGFR*-mutation positive NSCLC.[3] Tagrisso is noted as an

"preferred" option in the first-line setting. Upon disease progression, T790M testing is recommended in guidelines. NCCN added a footnote to this recommendation to also consider Gilotrif and Erbitux® (cetuximab for injection) combination regimen in patients with disease progression (T790M-negative multiple systemic lesions) on EGFR-TKI therapy (category 2A). This is based on data demonstrating similar response rates with this combination therapy in patients with T790M mutation-positive or mutation-negative tumors in pre-treated patients with NSCLC. NCCN notes that for squamous cell carcinoma, Gilotrif is not used in the second-line setting at NCCN institutions for these indications related to the efficacy and safety of these agents compared to the efficacy and safety of other available agents.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Gilotrif. All approvals are provided for 3 years in duration as noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Gilotrif is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Non-Small Cell Lung Cancer (NSCLC) – Epidermal Growth Factor Receptor (EGFR) Mutation-Positive.** Approve for 3 years if the patient meets the following criteria (A and B):
   ~~5.~~Patient has *metastatic* NSCLC; AND
   ~~6.~~ Patient has non-resistant *EGFR* mutation-positive NSCLC as detected by an approved test.

2. **Non-Small Cell Lung Cancer (NSCLC) – Squamous Cell Carcinoma.** Approve for 3 years if the patient meets the following criteria (A and B):
   A) Patient has metastatic squamous cell carcinoma; AND
   B) Patient has disease progression after treatment with platinum-based chemotherapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Gilotrif is not recommended in the following situations:

210. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

267. Gilotrif™ tablets [prescribing information]. Ridgefield, CT: Boehringer Ingelheim; October 2019.
2. The NCCN Drugs & Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 14, 2020. Search terms: afatinib.
3. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 1.2021 – November 25, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 14, 2020.

HISTORY

Type of Revision	Summary of Changes*	Review Date

Selected Revision	Deleted criteria requiring specific EGFR exon 19 or exon 21 mutations with regards to NSCLC. Based on FDA-approval, modified criteria to "non-resistant" EGFR mutation-positive NSCLC.	02/07/2018
Annual Revision	No criteria changes.	12/19/2018
Annual Revision	No criteria changes.	12/04/2019
Annual Revision	No criteria changes.	12/16/2020

EGFR – Epidermal growth factor receptor; NSCLC – Non-small cell lung cancer.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Ibrance Prior Authorization Policy
- Ibrance® (palbociclib capsules and tablets – Pfizer)

REVIEW DATE: 02/24/2021

OVERVIEW

Ibrance, a cyclin-dependent kinase (CDK) 4/6 inhibitor, is indicated for the treatment of adult patients with hormone receptor positive (**HR+**), human epidermal growth factor receptor 2 (**HER2**)-**negative advanced or metastatic breast cancer** in combination with:[1]

- An aromatase inhibitor (AI) as initial endocrine-based therapy in postmenopausal women or in men.
- Fulvestrant in patients with disease progression following endocrine therapy.

Guidelines

- **Breast Cancer:** The National Comprehensive Cancer Network (NCCN) guidelines on breast cancer (version 1.2021 – January 15, 2021) recommend any of the CDK4/6 inhibitors in combination with an AI or fulvestrant as a first-line preferred treatment option for recurrent or Stage IV HR+ and HER2-negative disease in postmenopausal women or premenopausal patient receiving ovarian ablation or suppression (category 1).[2,3] CDK4/6 inhibitor + fulvestrant is recommended for second- and subsequent-line therapy, if CDK4/6 inhibitor was not previously used (category 1). However, the guidelines also state in a footnote that if there is disease progression on CDK4/6 inhibitor therapy or PI3K inhibitor, there are limited data to support an additional line of therapy with another CDK4/6-containing regimen.[2,4] The compendium recommends that men with breast cancer be treated similarly to postmenopausal women, except that the use of an AI is ineffective without concomitant suppression of testicular steroidogenesis.[3]
- **Liposarcoma:** The NCCN guidelines on soft tissue sarcoma (version 6.2019 – February 10, 2020) recommend Ibrance as single-agent therapy for the treatment of well-differentiated/dedifferentiated liposarcoma (WD-DDLS) for retroperitoneal sarcomas (category 2A).[4]

Supportive Data

A multicenter analysis evaluated clinical outcomes in patients (n = 58) with HR+/HER2-negative metastatic breast cancer who received Verzenio (abemaciclib tablets) after disease progression on Ibrance or Kisqali (ribociclib tablets).[5] At data cutoff, 34% of patients (n = 20/58) had progressive disease, while 36% of patients (n = 21/58) had treatment duration exceeding 6 months. The median progression-free survival (PFS) was 5.8 months. Another case report of Verzenio use after 10 lines of therapy, including Ibrance therapy is available, along with literature review of ongoing studies with other CDK 4/6 inhibitors after prior use of another inhibitor.[6] Ibrance and Kisqali also have ongoing studies assessing for their respective efficacy after progression on another CDK4/6 inhibitor.[7,8] Preliminary results from the Kisqali trial (TRINITI-1), a Phase I/II, open-label trial of triplet therapy (Kisqali + everolimus + exemestane) after progression on prior CDK 4/6 inhibitor and up to three lines of therapy are available.[9] A total of 95 patients

were evaluated; 41.1% of patients demonstrated clinical benefit, exceeding the predefined primary endpoint threshold (> 10%). The response rate was 8.4% and the median PFS was 5.7 months, and the 1-year PFS was 33%.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ibrance. All approvals are provided for 3 years in duration unless otherwise noted below. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: a woman is defined as an individual with the biological traits of a woman, regardless of the individual's gender identity or gender expression; men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.
Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ibrance is recommended in those who meet the following criteria:

FDA-Approved Indications

55. Breast Cancer in Postmenopausal Women*. Approve for 3 years if the patient meets the following criteria (A, B, and C):
- **7.** Patient has advanced or metastatic hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND
- **8.** Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
- **9.** Patient meets ONE of the following criteria (i or ii):
  - **i.** Ibrance will be used in combination with anastrozole, exemestane, or letrozole; OR
  - **ii.** Ibrance will be used in combination with fulvestrant.

***** Refer to the Policy Statement.

2. Breast Cancer in Pre/Perimenopausal Women*. Approve for 3 years if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient has advanced or metastatic hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND
- **B)** Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
- **C)** Patient is receiving ovarian suppression/ablation with a gonadotropin-releasing hormone (GnRH) agonist or has had surgical bilateral oophorectomy or ovarian irradiation; AND
  Note: Examples are Lupron (leuprolide), Trelstar (triptorelin), Zoladex (goserelin).
- **D)** Patient meets ONE of the following conditions (i or ii):
  - **i.** Ibrance will be used in combination with anastrozole, exemestane, or letrozole; OR
  - **ii.** Ibrance will be used in combination with fulvestrant.

***** Refer to the Policy Statement.

3. Breast Cancer in Men*. Approve for 3 years if the patient meets the following criteria (A, B, and C):
- **A)** Patient has advanced or metastatic hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND
- **B)** Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
- **C)** Patient meets ONE of the following criteria (i or ii):

i. Patient meets BOTH of the following criteria (a and b):
  a) Patient is receiving a gonadotropin-releasing hormone (GnRH) analog; AND
  Note: Examples are Lupron (leuprolide), Trelstar (triptorelin), Zoladex (goserelin), Firmagon (degarelix), Orgovyx (relugolix).
  b) Ibrance will be used in combination with anastrozole, exemestane, or letrozole; OR
ii. Ibrance will be used in combination with fulvestrant.

***** Refer to the Policy Statement.

Other Uses with Supportive Evidence

4. Liposarcoma. Approve for 3 years if the patient has well-differentiated/dedifferentiated liposarcoma (WD-DDLS).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ibrance is not recommended in the following situations:

211. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

268. Ibrance® capsules and tablets [prescribing information]. New York, NY: Pfizer Labs; November 2019.
269. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 1.2021 – January 15, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 21, 2021.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Deleted criteria in all approval conditions which require patient to try a prior endocrine therapy before approving for Ibrance + Faslodex. Likewise, deleted criteria that required Ibrance + aromatase inhibitors use (e.g., letrozole) only as initial therapy. Guidelines support first-line or subsequent therapy use.	04/03/2019
Annual Revision	Added Ibrance "tablets" to drug targets. Use of Ibrance in men is an FDA approved use, so moved it under "FDA-approved Indications".	04/15/2020
Early Annual Revision	**All Breast Cancer Indications:** Deleted criteria requiring no disease progression on Kisqali (ribociclib), Ibrance, or Verzenio (abemaciclib), based on guidelines and available data. **Breast Cancer in Pre/Perimenopausal Women:** Examples of gonadotropin-releasing hormone (GnRH) agonists are moved from criteria to Note. **Breast Cancer in Men:** GnRH "agonist" is changed to "analog". Also, the list of examples of GnRH analog agents are moved from criteria to Note. Firmagon (degarelix) and Orgovyx (relugolix) were added to example list.	02/24/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Iclusig Prior Authorization Policy

- Iclusig® (ponatinib tablets – ARIAD/Takeda)

REVIEW DATE: 04/01/2020

OVERVIEW

Iclusig, a tyrosine kinase inhibitor (TKI), is indicated for the treatment of adults with T315I-positive chronic myeloid leukemia (CML) [chronic phase {CP}, accelerated phase {AP}, or blast phase {BP}] and T135I-positive Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL).[1] Iclusig is also indicated for the treatment of adults with CP, AP, or BP CML or Ph+ ALL for whom no other TKI therapy is indicated. A limitation of use is that Iclusig is not indicated and is not recommended for the treatment of patients with newly-diagnosed chronic phase CML. There are four other TKIs approved for the treatment of Ph+ CML: Gleevec® (imatinib tablets, generic), Sprycel® (dasatinib tablets), Tasigna® (nilotinib capsules), and Bosulif® (bosutinib tablets).[5-8] These agents are indicated for the treatment of Ph+ CML in various phases; some TKIs are indicated after resistance or intolerance to prior therapy. Sprycel and Gleevec are also indicated for use in patients with Ph+ ALL.[5,6]

Clinical Efficacy

The PACE (Ponatinib Ph+ ALL and CML Evaluation) trial was a Phase II, open-label, multinational study that assessed Iclusig in patients with CML or Ph+ ALL (n = 449) who were heavily pretreated with resistance to or unacceptable adverse effects with Sprycel® (dasatinib tablets) or Tasigna® (nilotinib capsules) or who had the BCR-ABL T315I mutation.[1,2] Benefits (e.g., major cytogenetic response, complete cytogenetic response) were noted in many patients.[2] A Phase I, dose-escalation trial (n = 81) investigated Iclusig in patients with resistant hematologic cancer including CML and Ph+ ALL.[3] Results suggest that Iclusig was highly active in heavily pretreated patients with Ph+ leukemias with resistance to TKI inhibitors, including patients with the BCR-ABL T315I mutation, other mutations, or no mutations. Other data are also available.[11,12]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for CML (version 3.2020 – January 30, 2020) state that for patients with CP CML with a low-risk score, the primary treatment recommended includes a first-generation TKI (Gleevec or generic imatinib 400 mg QD [Category 1]), or a second-generation TKI (Bosulif 400 mg QD [Category 1], Sprycel 100 mg QD [Category 1], or Tasigna 300 mg BID [Category 1]).[9] For patients with CP CML with an intermediate- or high-risk score, a second-generation TKI is preferred (Bosulif 400 mg QD [Category 1], Sprycel 100 mg QD [Category 1], or Tasigna 300 mg BID [Category 1]). A first-generation TKI (Gleevec or generic imatinib 400 mg QD) is an alternative [Category 2A]. Iclusig is an option for patients with a T315I mutation and for with disease that has not responded to multiple TKIs or in whom another TKI is not indicated. The NCCN guidelines

for ALL (adult and adolescent young adults) [version 1.2020 – January 15, 2020] recommend Iclusig as an option for patients with relapsed or refractory ALL and note its activity against T315I mutations.[10]

Safety

Iclusig has a Boxed Warning regarding arterial occlusion, venous thromboembolism, heart failure and hepatotoxicity.[1] The dosage and administration section notes that the optimal dose of Iclusig has not been identified. In clinical trials, the initial dose of Iclusig was 45 mg once daily (QD). However, many patients (68%) required dose reductions to 30 mg to 15 mg QD during the therapy course. Consideration should be given to discontinue Iclusig if a response has not occurred by 3 months (90 days). Iclusig has a Risk Evaluation and Mitigation Strategy (REMS) program.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Iclusig. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Iclusig is recommended in those who meet the following criteria:

FDA-Approved Indications

56. Chronic Myeloid Leukemia (CML) That is Philadelphia Chromosome Positive. Approve for 3 years if the patient meets one of the following criteria (A or B):

A) The patient is T315I-positive, OR

B) The patient has tried at least two other tyrosine kinase inhibitors indicated for use in Philadelphia chromosome positive CML.
Note: Examples include Gleevec® (imatinib tablets), Sprycel® (dasatinib tablets), and Tasigna® (nilotinib capsules).

57. Acute Lymphoblastic Leukemia (ALL) That is Philadelphia Chromosome Positive (Ph+). Approve for 3 years if the patient meets ONE of the following criteria (A or B):

C) The patient is T315I-positive; OR

D) The patient has tried at least two other tyrosine kinase inhibitors that are used for Philadelphia chromosome positive ALL.
Note: Examples include Gleevec® (imatinib tablets), and Sprycel® (dasatinib tablets).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Iclusig is not recommended in the following situations:

212. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	Removed the criteria allowing for approval if the patient has been started on Iclusig for an indication or condition addressed as an approval in the Recommended Authorization section.	03/07/2018
Annual revision	No criteria changes.	03/20/2019
Annual revision	The following changes was made: **Chronic Myeloid Leukemia that is Ph+:** The wording that the patient has tried two other tyrosine kinase inhibitors for chronic myeloid leukemia was changed to state "at least two" and examples of tyrosine kinase inhibitors were moved from the criteria to a note. **Acute Lymphoblastic Leukemia that is Ph+:** The wording that the patient has tried two other tyrosine kinase inhibitors for acute lymphoblastic leukemia was changed to state "at least two" and examples of tyrosine kinase inhibitors were moved from the criteria to a note.	04/01/2020

Ph+ – Philadelphia chromosome positive.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Idhifa Prior Authorization Policy
- Idhifa® (ensidenib tablets – Celgene/Agios)

REVIEW DATE: 02/10/2021

OVERVIEW

Idhifa, an isocitrate dehydrogenase-2 (IDH2) inhibitor, is indicated for the treatment of relapsed or refractory acute myeloid leukemia (AML) in adults with an IDH2 mutation as detected by an FDA-approved test.[1]

Disease Overview

AML is a heterogeneous hematologic malignancy characterized by clonal expansion of myeloid blasts in the peripheral blood, bone marrow, and/or other tissues.[2] Undifferentiated blast cells proliferate in bone marrow instead of maturing into normal blood cells. Among adults, it is the most common form of acute leukemia and accounts for the largest number of annual deaths from leukemias in the US. An estimated 19,940 individuals will be diagnosed with AML in 2019 and 11,180 are projected to die from the condition. The median age at diagnosis is 67 years. Diagnosis occurs at ≥ 65 years of age for 54% of patients with around one-third of patients diagnosed at ≥ 75 years of age. The incidence of AML increase as the population ages. Environmental factors such as prolonged exposure to petrochemicals, solvents such as benzene, pesticides, and ionizing radiation have been established to increase the risks for AML, as well as myelodysplastic syndrome (MDS).[2] The cure rates of AML have improved with this outcome noted in

35% to 40% of adult patients who are ≤ 60 years of age and 5% to 15% for patients who are > 60 years of age.[3] However, among patients who are older and unable to receive intensive chemotherapy the survival rates are dismal with a median survival of only 5 to 10 months. Various gene mutations are present in adults with AML. The incidence of IDH2 mutations increase with advancing age.[3] IDH2 mutations have been reported in up to 12% of patients with AML.[2] Mutations have been identified in R172 and R140 of the IDH2 gene with the R140 mutation more frequently occurring.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on AML (version 2.2021 – November 12, 2020) note Idhifa as an alternative for IDH2 mutated AML in a variety of clinical scenarios. Idhifa is recommended for patients who have relapsed or refractory disease who have the IDH2 mutation. Another clinical scenario is for treatment induction among patients ≥ 60 years of age who are not a candidate for intensive remission induction therapy or declines such therapy. In patients ≥ 60 years of age who had a response to previous lower intensity therapy, Idhifa can be continued. Both clinical scenarios apply to patients who are IDH2 mutation positive.

Safety

Idhifa has a Boxed Warning regarding differentiation syndrome.[1]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Idhifa. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Idhifa is recommended in those who meet the following criteria:

FDA-Approved Indication

58. Acute Myeloid Leukemia (AML). Approve for 3 years if the disease is isocitrate dehydrogenase-2 (IDH2)-mutation positive as detected by an approved test.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Idhifa is not recommended in the following situations:

213. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	Added criteria to approve if the patient is IDH2 mutation-positive "as detected by an approved test".	02/06/2019
Annual Revision	No criteria changes.	02/05/2020
Annual Revision	No criteria changes.	02/10/2021

IDH2 – Isocitrate dehydrogenase-2.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Imatinib (Gleevec) Prior Authorization Policy

- Imatinib (Gleevec) [imatinib mesylate tablets for oral use – Novartis, generic]

REVIEW DATE: 04/01/2020

OVERVIEW

Imatinib, a tyrosine kinase inhibitor (TKI), is indicated for the treatment of: newly-diagnosed adult and pediatric patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase (CP); Ph+ CML in blast crisis (BC), accelerated phase (AP) or in CP after failure of interferon-alpha therapy; adult patients with relapsed or refractory Ph+ acute lymphoblastic leukemia (ALL); pediatric patients with newly-diagnosed Ph+ positive ALL in combination with chemotherapy, adults with myelodysplastic/myeloproliferative disease (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene rearrangements; adults with aggressive systemic mastocytosis (ASM); adults with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL); adults with unresectable, recurrent, and/or metastatic dermatofibrosarcoma protuberans (DFSP); patients with Kit (CD 117) positive unresectable and/or metastatic gastrointestinal stromal tumors (GIST); and as adjuvant treatment of adults following resection of Kit (CD117) positive GIST.[1] Imatinib is also available as a generic but it does not have any indications regarding GIST, now the indication for use in pediatric patients with ALL.[2] Currently, there are four other tyrosine kinase inhibitors (TKIs) approved for the treatment of Ph+ CML: Tasigna® (nilotinib capsules), Sprycel® (dasatinib tablets), Bosulif® (bosutinib tablets), and Iclusig® (ponatinib tablets).[3-6] These agents are indicated for the treatment of Ph+ CML in various phases. Iclusig is approved for patients with T315I-positive CML and in adult patients with CML for whom no other TKI therapy is indicated.[6] Sprycel also has FDA-approved indications regarding ALL.[3]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for CML (version 3.2020 – January 30, 2020) state that for patients with CP CML with a low-risk score, the primary treatment recommended includes a first-generation TKI (Gleevec or generic imatinib 400 mg QD [Category 1]), or a second-generation TKI (Bosulif 400 mg QD [Category 1], Sprycel 100 mg QD [Category 1], or Tasigna 300 mg BID [Category 1]).[7] For patients with CP CML with an intermediate- or high-risk score, a second-generation TKI is preferred (Bosulif 400 mg QD [Category 1], Sprycel 100 mg QD [Category 1], or Tasigna 300 mg BID [Category 1]). A first-generation TKI (Gleevec or generic imatinib 400 mg QD) is an alternative [Category 2A]. Iclusig is an option for patients with a T315I mutation and for with disease that has not responded to multiple TKIs or in whom another TKI is not indicated.

The NCCN guidelines for ALL (adults and adolescent young adults) [version 1.2020 – January 15, 2020][8] and Pediatric ALL (pediatric and adolescent young adults) [version 2.2020 – November 25, 2019][9] recommend imatinib in a variety of clinical scenarios including induction therapy, maintenance, relapsed or refractory ALL and for use in specific mutations.

The NCCN guidelines on dermatofibrosarcoma protuberans (version 1.2020 – October 2, 2019)[10] recommend to consider imatinib in certain cases such as where disease is unresectable, or unacceptable functional or adverse cosmetic outcomes may occur with resection. Of note, the guidelines state that because tumors lacking the t(17;22) translocation may not respond to imatinib, molecular analysis of a tumor using cytogenetics may be useful before initiating imatinib therapy.

The NCCN guidelines on soft tissue sarcoma (version 6.2019 – February 10, 2020) address GIST.[11] GISTs can occur anywhere along the gastrointestinal (GI) tract, but most commonly occur in the stomach and small intestine due to activating mutations in KIT (CD117). Surgery is the primary treatment for patients with resectable GIST; however, this is not always curative or cannot be done. Imatinib is recommended in various clinical settings, including preoperatively, postoperatively, as a primary therapy, as well as for patients with locally advanced or previously unresectable tumors. Imatinib is considered a primary therapy for metastatic GIST.

The NCCN guidelines on myelodysplastic syndromes (MDS) [version 2.2020 – February 28, 2020] note that data have demonstrated that patients with chronic myelomonocytic leukemia (CMML)/myeloproliferative disease (MPD) who have PDGFRβ fusion genes may respond well to imatinib.[12]

The NCCN guidelines for systemic mastocytosis (version 2.2019 – September 20, 2018) recommend imatinib (only if KITD816V mutation negative or unknown or if eosinophilia is present with FIP1L1-PDGFRA fusion gene).[13]

The NCCN guidelines for acquired immune deficiency syndrome (AIDS)-Related Kaposi Sarcoma (version 1.2020 – February 12, 2020) recommended imatinib for subsequent systemic therapy options for relapsed/refractory therapy.[14] First-line systemic therapy options include liposomal doxorubicin (preferred), and paclitaxel. Other subsequent systemic therapy options for relapsed/refractory therapy are also cited (e.g., Pomalyst® [pomalidomide capsules] {preferred], Revlimid® [lenalidomide capsules], Thalomid [thalidomide capsules]).

The NCCN guidelines on bone cancer (version 1.2020 – August 12, 2019) state that imatinib, either as monotherapy or in combination with cisplatin or Rapamune® (sirolimus tablets), is recommended for treatment of chordoma.[15]

The NCCN guidelines on soft tissue sarcoma (version 6.2019 – February 10, 2020) have included non-steroidal anti-inflammatory drugs (NSAIDs), hormonal or biologic agents (tamoxifen, Fareston® [toremifene tablets], or low-dose interferon), chemotherapy (methotrexate and vinorelbine, doxorubicin-based regimens), and TKIs (imatinib and Nexavar® [sorafenib tablets]) as options for systemic therapy for patients with advanced or unresectable desmoid tumors (aggressive fibromatosis).[11]

The NCCN has guidelines regarding hematopoietic cell transplantation (version 1.2020 – October 30, 2019) that address GVHD.[16] Imatinib is cited as one of many therapies recommended for steroid-refractory, chronic GVHD. Some other agents include Imbruvica® (ibrutinib tablets and capsules), low-dose methotrexate, sirolimus, mycophenoate mofetil, Jakafi® (ruxolitinib tablets).

The NCCN guidelines on cutaneous melanoma (version 1.2020 – December 19, 2019) cite imatinib as useful in certain scenarios as systemic therapy for metastatic or resectable disease such as for tumors with activating mutations of KIT.[17]

The NCCN guidelines on soft tissue sarcoma (version 6.2019 – February 10, 2020) cite Turalio (pexidartinib capsules) [category 1] and imatinib (category 2A) as systemic therapies with activity in PVNS/TGCT.[11]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Gleevec and generic imatinib mesylate tablets. If the patient does not meet the criteria regarding brand Gleevec, auto-approvals will be given for generic imatinib mesylate tablets when patients meet conditions for coverage of imatinib as defined in this policy. All approvals are provided for the duration noted below.

Automation: None.

Documentation: In the imatinib (Gleevec) PA, documentation is required for use of generic imatinib as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts and/or other information.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Gleevec and generic imatinib mesylate tablets are recommended in those who meet the following criteria:

FDA-Approved Indications

3. **Acute Lymphoblastic Leukemia (ALL) That is Philadelphia Chromosome Positive (Ph+).** Approve for 3 years if the patient meets one of the following criteria (A or B):
   - **A)** Generic imatinib mesylate tablets are requested; OR
   - **B)** If brand Gleevec is prescribed, the patient has tried generic imatinib mesylate tablets AND cannot take generic imatinib mesylate tablets due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescribing physician, would result in a significant allergy or serious adverse reaction **[documentation required]**.

4. **Chronic Myeloid Leukemia (CML) That is Philadelphia Chromosome Positive (Ph+).** Approve for 3 years if the patient meets one of the following criteria (A or B):
   - **A)** Generic imatinib mesylate tablets are requested; OR
   - **B)** If brand Gleevec is prescribed, the patient has tried generic imatinib mesylate tablets AND cannot take generic imatinib mesylate tablets due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescribing physician, would result in a significant allergy or serious adverse reaction **[documentation required]**.

5. **Dermatofibrosarcoma Protuberans (DFSP).** Approve for 3 years if the patient meets one of the following criteria (A or B):
   - **A)** Generic imatinib mesylate tablets are requested; OR
   - **B)** If brand Gleevec is prescribed, the patient has tried generic imatinib mesylate tablets AND cannot take generic imatinib mesylate tablets due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescribing physician, would result in a significant allergy or serious adverse reaction **[documentation required]**.

6. **Gastrointestinal Stromal Tumors (GIST).** Approve for 3 years if the patient meets one of the following criteria (A or B):
   - **A)** Generic imatinib mesylate tablets are requested; OR
   - **B)** If brand Gleevec is prescribed, the patient has tried generic imatinib mesylate tablets AND cannot take generic imatinib mesylate tablets due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescribing physician, would result in a significant allergy or serious adverse reaction **[documentation required]**.

7. **Hypereosinophilic Syndrome (HES) and/or Chronic Eosinophilic Leukemia (CEL).** Approve for 3 years if the patient meets one of the following criteria (A or B):
   - **A)** Generic imatinib mesylate tablets are requested; OR
   - **B)** If brand Gleevec is prescribed, the patient has tried generic imatinib mesylate tablets AND cannot take generic imatinib mesylate tablets due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescribing physician, would result in a significant allergy or serious adverse reaction **[documentation required]**.

8. **Aggressive Systemic Mastocytosis (ASM).** Approve for 3 years if the patient meets one of the following criteria (A or B):
   - **A)** Generic imatinib mesylate tablets are requested; OR
   - **B)** If brand Gleevec is prescribed, the patient has tried generic imatinib mesylate tablets AND cannot take generic imatinib mesylate tablets due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescribing physician, would result in a significant allergy or serious adverse reaction **[documentation required]**.

9. **Myelodysplastic/Myeloproliferative Disease (MDS/MPD) [e.g., polycythemia vera, myelofibrosis].** Approve for 3 years if the patient meets the following criteria (A and B):
   - **A)** The condition is associated with platelet-derived growth factor receptor (PDGFR) gene rearrangements; AND
   - **B)** The patient meets one of the following criteria (i or ii):
     - **i.** Generic imatinib mesylate tablets are requested; OR
     - **ii.** If brand Gleevec is prescribed, the patient has tried generic imatinib mesylate tablets AND cannot take generic imatinib mesylate tablets due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescribing physician, would result in a significant allergy or serious adverse reaction **[documentation required]**.

Other Uses with Supportive Evidence

10. **Acquired Immune Deficiency Syndrome (AIDS)-Related Kaposi's Sarcoma.** Approve for 3 years if the patient meets the following criteria (A, B and C):
    - **A)** The patient has tried at least one regimen or therapy; AND
      Note: Examples include liposomal doxorubicin, paclitaxel, Pomalyst® (pomalidomide capsules), Revlimid® (lenalidomide capsules), etoposide, and Thalomid® (thalidomide capsules).
    - **B)** The patient has relapsed or refractory disease; AND
    - **C)** The patient meets one of the following criteria (i or ii):
      - **i.** Generic imatinib mesylate tablets are requested; OR
      - **ii.** If brand Gleevec is prescribed, the patient has tried generic imatinib mesylate tablets AND cannot take generic imatinib mesylate tablets due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescribing physician, would result in a significant allergy or serious adverse reaction **[documentation required]**.

11. **Chordoma.** Approve for 3 years if the patient meets one of the following criteria (A or B):
    - **A)** Generic imatinib mesylate tablets are requested; OR
    - **B)** If brand Gleevec is prescribed, the patient has tried generic imatinib mesylate tablets AND cannot take generic imatinib mesylate tablets due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescribing physician, would result in a significant allergy or serious adverse reaction **[documentation required]**.

12. **Fibromatosis (Desmoid Tumors).** Approve for 3 years if the patient meets the following criteria (A and B):
    - **A)** The patient has advanced or unresectable fibromatosis (desmoid tumors); AND
    - **B)** The patient meets one of the following criteria (i or ii):
      - **i.** Generic imatinib mesylate tablets are requested; OR
      - **ii.** If brand Gleevec is prescribed, the patient has tried generic imatinib mesylate tablets AND cannot take generic imatinib mesylate tablets due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescribing physician, would result in a significant allergy or serious adverse reaction **[documentation required]**.

13. **Graft Versus Host Disease (GVHD), Chronic.** Approve for 1 year if the patient meets the following criteria (A and B):
    - **A)** The patient has tried at least one conventional systemic treatment for graft versus host disease; AND
      Note: Examples include corticosteroids (methylprednisolone, prednisone); cyclosporine; tacrolimus; mycophenolate mofetil; Imbruvica® (ibrutinib capsules and tablets); low-dose methotrexate; sirolimus; and Jakafi® (ruxolitinib tablets).
    - **B)** The patient meets one of the following criteria (i or ii):
      - **i.** Generic imatinib mesylate tablets are requested; OR
      - **ii.** If brand Gleevec is prescribed, the patient has tried generic imatinib mesylate tablets AND cannot take generic imatinib mesylate tablets due to a formulation difference in the inactive ingredient(s) [e.g.,

difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescribing physician, would result in a significant allergy or serious adverse reaction **[documentation required]**.

14. Metastatic Melanoma: Approve for 3 years if the patient meets the following criteria (A and B):
- **A)** The patient has c-Kit-positive advanced/recurrent or metastatic melanoma; AND
- **B)** The patient meets one the following criteria (i or ii):
  - **i.** Generic imatinib mesylate tablets are requested; OR
  - **ii.** If brand Gleevec is prescribed, the patient has tried generic imatinib mesylate tablets AND cannot take generic imatinib mesylate tablets due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescribing physician, would result in a significant allergy or serious adverse reaction **[documentation required]**.

15. Pigmented Villonodular Synovitis/Tenosynovial Giant Cell Tumor (PVNS/TGCT). Approve for 3 years if the patient meets both of the following criteria (A and B):
- **A)** The patient meets one of the following (i or ii):
  - **i.** The patient has tried Turalio (pexidartinib capsules); OR
  - **ii.** According to the prescriber, the patient cannot take Turalio.

  Note: Examples of reasons for not being able to take Turalio include patients with elevated liver enzymes or concomitant use of medications that are associated with hepatotoxicity; AND
- **B)** The patient meets one of the following (i or ii):
  - **i.** Generic imatinib mesylate tablet are requested; OR
  - **ii.** If brand Gleevec is prescribed, the patient has tried generic imatinib mesylate tablets AND cannot take generic imatinib mesylate tablets due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the bioequivalent generic product which, per the prescribing physician, would result in a significant allergy or serious adverse reaction **[documentation required]**.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of imatinib is recommended in those who meet the following criteria:

214. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

298. Gleevec® tablets [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals, Inc.; July 2018.
299. Imatinib tablets [prescribing information]. Cranbury, NJ and Jacksonville, FL: Sun Pharmaceuticals and Ranbaxy Pharmaceuticals; October 2016.
300. Tasigna® capsules [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals, Inc.; September 2019.
301. Sprycel® tablets [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; December 2018.
302. Bosulif® tablets [prescribing information]. New York, NY: Pfizer Inc; October 2019.
303. Iclusig® tablets [prescribing information]. Cambridge, MA: Takeda/Ariad Pharmaceuticals; January 2020.
304. The NCCN Chronic Myeloid Leukemia Clinical Practice Guidelines in Oncology (Version 3.2020 – January 30, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 17, 2020.
305. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (Version 1.2020 – January 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 17, 2020.
306. The NCCN Pediatric Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 2.2020 – November 25, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 17, 2020.
307. The NCCN Dermatofibrosarcoma Protuberans Clinical Practice Guidelines in Oncology (Version 1.2020 – October 2, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 18, 2020.
308. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (version 6.2019 – February 10, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 18, 2020.
309. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (Version 2.2020 – February 28, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 17, 2020.

310. The NCCN Systemic Mastocytosis Clinical Practice Guidelines in Oncology (version 2.2019 – September 20, 2018). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 18, 2020.
311. The NCCN AIDS-Related Kaposi Sarcoma Clinical Practice Guidelines in Oncology (Version 1.2020 – February 12, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 18, 2020.
312. The NCCN Bone Cancer Clinical Practice Guidelines in Oncology (Version 1.2020 – August 12, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 18, 2020.
313. The NCCN Hematopoietic Cell Transplantation (HCT): Pre-Transplantation Recipient Evaluation and Management of Graft-Versus-Host Disease (version 1.2020 – October 30, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 18, 2020.
314. The NCCN Cutaneous Melanoma Clinical Practice Guidelines in Oncology (Version 1.2020 – December 19, 2020). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 18, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	The policy was renamed from Oncology – Gleevec to Oncology – Imatinib (Gleevec) to reflect the generic availability of Gleevec. Criteria were developed for patients with AIDS-related Kaposi Sarcoma to approve for 3 years if the patient has tried one other therapy, has relapsed or refractory disease, and either requests the generic or has experienced certain issues with the generic the patient has tried one systemic therapy. The exclusion for Kaposi Sarcoma was removed.	03/20/2019
Annual Revision	The following changes were made. 1. **Acquired Immune Deficiency Syndrome-Related Kaposi's Sarcoma:** The criteria that requires a trial of one regimen now states "at least one regimen" and the alternatives are now listed as a note instead of in the criteria. 2. **Graft Versus Host Disease, Chronic:** The criteria that requires a trial of one conventional systemic treatment was changed to state "at least one" and the alternatives are now listed as a note instead of in the criteria. 3. **Pigmented Villonodular Synovitis/Tenosynovial Giant Cell Tumor:** Criteria were added that the patient has tried Turalio or according to the prescriber the patient cannot take Turalio. A note was added that reasons for not being able to take Turalio include patients with elevated liver enzymes or concomitant use of medications that are associated with hepatotoxicity. 4. **Other Conditions Not Recommended for Approval:** The following conditions were removed from this section: acute myeloid leukemia; advanced salivary adenoid cystic carcinoma; biliary tract cancer; breast cancer; central nervous system tumors; cervical cancer; chondrosarcoma; head and neck squamous cell carcinoma; hepatocellular carcinoma; idiopathic pulmonary fibrosis; meningioma; merkel cell carcinoma; mesothelioma; multiple myeloma; non-small cell lung cancer (metastatic); ovary/peritoneum, or fallopian tube (carcinoma of); pancreatic adenocarcinoma; prostate cancer; pulmonary arterial hypertension; renal cell carcinoma; restenosis; sarcoma; scleroderma; scleroderma-related interstitial lung disease; small cell lung cancer; spondyloarthritis; testicular cancer/germ cell tumors; thymic epithelial malignancies; thyroid cancer; and uterine carcinosarcomas. Reason for removal include lack of requests for use, limited recent literature, availability of other medications, and/or the conditions are not addressed in related guidelines by the NCCN.	04/01/2020

AIDS – Acquired immunodeficiency syndrome; NCCN – National Comprehensive Cancer Network.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Imbruvica Prior Authorization Policy

- Imbruvica® (ibrutinib tablets and capsules – Pharmacyclics/Janssen)

REVIEW DATE: 06/03/2020

OVERVIEW

Imbruvica, a Bruton kinase inhibitor, is indicated for the treatment mantle cell lymphoma in adults with who have received at least one prior therapy.[1] Accelerated approval for this indication was granted based on overall response rate. Continued approval for this condition may be contingent on verification of clinical benefit in confirmatory trials. Imbruvica is also indicated for the treatment chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) in adults. Regarding CLL and SLL, Imbruvica is also indicated for the treatment of 17p deletion CLL and SLL in adults. Imbruvica is also indicated for the treatment Waldenström's macroglobulinemia in adults. Imbruvica is indicated for the treatment of marginal zone lymphoma in adults with who require systemic therapy and have received at least one prior anti-CD20-based therapy. Accelerated approval was granted for this indication was based on the overall response rate. Continued approval may be based contingent upon verification and description of clinical benefit in a confirmatory trial. Imbruvica is also indicated for the treatment of chronic graft-versus-host disease (GVHD) in adults with after failure of one or more lines of systemic therapy.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for CLL/SLL (version 4.2020 – December 20, 2019) recommend Imbruvica as a treatment option in various scenarios (e.g., first-line therapy for patients with or without deletion 17p/TP53 mutation; and as relapsed/refractory therapy [category 1 recommendations for many scenarios]).[2] Imbruvica plays a vital role in the management of CLL/SLL and many trials describe its efficacy.

The NCCN guidelines for B-Cell Lymphomas (version 1.2020 – January 22, 2020) address mantle cell lymphoma.[3] Imbruvica is recommended as a one of the preferred second-line therapies, with or without rituximab (category 2A).

The NCCN guidelines for B-Cell Lymphomas (version 1.2020 – January 22, 2020) address marginal zone lymphoma.[3] Preferred first-line regimens include use of rituximab with other agents. Imbruvica is cited as an option as a second-line and subsequent therapy.

The NCCN guidelines for Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphomas (version 2.2020 – April 15, 2020) recommend Imbruvica, with or without rituximab, as a primary therapy option as one of several preferred regimens (category 2).[4] For previously treated patients Imbruvica, with or without rituximab, is also cited as a preferred regimen.

The NCCN guidelines for Central Nervous System (CNS) Cancers B-Cell Lymphomas (version 2.2020 – April 30, 2020) recommend Imbruvica as one of the options for patients with relapsed or refractory disease.[5] In some clinical scenarios it is used with rituximab.

The NCCN guidelines for Hairy Cell Leukemia (version 1.2020 – August 23, 2019) recommend Imbruvica as one of the options for patients with relapsed or refractory disease following progression.[6]

The NCCN guidelines for B-Cell Lymphomas (version 1.2020 – January 22, 2020) address diffuse large B-cell lymphoma.[3] Imbruvica is cited as a second-line and subsequent therapy. Other therapy regimens are recommended first-line, many of which are rituximab-based.

The NCCN has guidelines regarding hematopoietic cell transplantation (version 1.2020 – October 30, 2019) that address GVHD.[8] Imbruvica is cited as one of many therapies recommended for steroid-refractory, chronic GVHD. Some other agents include imatinib, low-dose methotrexate, sirolimus, mycophenoate mofetil, Jakafi® (ruxolitinib tablets). Data are also available for Imbruvica.[9]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Imbruvica. All approvals are provided for the duration noted below.

Automation: When available, the ICD-9/ICD-10 codes for chronic lymphocytic leukemia (CLL) (ICD-9: 204.1* [lymphoid leukemia chronic] and ICD-10: C91.1* [chronic lymphocytic leukemia of B-cell type]), Mantle Cell Lymphoma (ICD-9: 200.4* and ICD-10: C83.1*), Small Lymphocytic Lymphoma (ICD-10: C83.0* [small cell B-cell lymphoma]) and Waldenström's macroglobulinemia (ICD-9: 273.3* [macroglobulinemia] and ICD-10: C88.0*) will be used as part of automation to allow approval of the requested medication.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Imbruvica is recommended in those who meet the following criteria:

FDA-Approved Indications

59. Chronic Lymphocytic Leukemia (CLL). Approve for 3 years.

60. Mantle Cell Lymphoma. Approve for 3 years.

61. Marginal Zone Lymphoma. Approve for 3 years.

62. Small Lymphocytic Lymphoma (SLL). Approve for 3 years.

63. Waldenström's Macroglobulinemia. Approve for 3 years.

64. Graft versus Host Disease, Chronic: Approve for 1 year if the patient has tried at least one conventional systemic treatment for graft versus host disease.
Note: Examples include corticosteroids (methylprednisolone, prednisone), imatinib, low-dose methotrexate, sirolimus, mycophenolate mofetil, and Jakafi® (ruxolitinib tablets).

Other Uses with Supportive Evidence

215. Central Nervous System (CNS) Lymphoma (Primary). Approve for 3 years if according to the prescribing physician the patient has relapsed or refractory disease.

216. B-Cell Lymphoma. Approve for 3 years if according to the prescribing physician the patient is using the agent as second-line or subsequent therapy.
Note: Examples of B-Cell Lymphomas include follicular lymphoma, diffuse large B-cell lymphomas, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, nongastric MALT lymphoma, Acquired Immune Deficiency Syndrome (AIDS)-related, and post-transplant lymphoproliferative disorders.

217. Hairy Cell Leukemia. Approve for 3 years if the according to the prescribing physician the patient has relapsed or refractory disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Imbruvica is recommended in those who meet the following criteria:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

315. Imbruvica® tablets and capsules [prescribing information]. Sunnyvale, CA and Horsham, PA: Pharmacyclics and Janssen Biotech; April 2020.
316. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (Version 4.2020 – December 20, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at http://www.nccn.org. Accessed on May 29, 2020.
317. The NCCN B-cell Lymphomas Guidelines in Oncology (Version 1.2020 – January 22, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 29, 2020.
318. The NCCN Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma Clinical Practice Guidelines in Oncology (Version 2.2020 – April 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 29, 2020.
319. The NCCN Central Nervous System Cancers Guidelines in Oncology (Version 2.2020 – April 30, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 29, 2020.
320. The NCCN Hairy Cell Leukemia Guidelines in Oncology (Version 1.2020 – August 23, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 29, 2020.
321. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenström's Macroglobulinemia. *N Engl J Med*. 2015;372(15):1430-1440.
322. The NCCN Hematopoietic Cell Transplantation (HCT): Pre-Transplantation Recipient Evaluation and Management of Graft-Versus-Host Disease (version 2.2020 – March 23, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 29, 2020.
323. Miklos D, Cutler CS, Arora M, et al. Ibrutinib for chronic graft-versus-host disease after failure or prior therapy. *Blood*. 2017;130(21):2243-2250.

HISTORY

Type of Revision	Summary of Change	Review Date
Annual Revision	Added approvals under the "Other Uses with Supportive Evidence" section, for hairy cell leukemia, DLBCL, and central nervous system lymphoma (primary) per recommendations by the respective NCCN guidelines.	05/16/2018
Annual Revision	The following changes were made: **1. Marginal Zone Lymphoma:** The requirement that the patient has tried rituximab, or according to the prescribing physician rituximab is contraindicated, was removed. **2. Graft Versus Host Disease, Chronic:** For clarity, Jakafi was added to the list of examples of conventional systemic agents, one of which must be tried prior to approval of Imbruvica. **3. B-Cell Lymphoma:** The condition was changed to as listed; previously listed as "Diffuse Large B-Cell Lymphoma". Autoimmune Deficiency Syndrome-related and post-transplant lymphoproliferative disorder were added to the examples of B-Cell Lymphoma. The listing of primary diffuse large B-cell lymphoma of the central nervous system was deleted as it is addressed in a different criterion.	06/05/2019
Annual Revision	The following changes were made. **1. Graft Versus Host Disease, Chronic:** The descriptor of "at least" was added to the criterion that requires that the patient has tried one conventional systemic treatment for graft vs. host disease. Also, examples of treatments were moved from the criteria to a note with examples of low-dose methotrexate and sirolimus added and tacrolimus removed. **2. B-Cell Lymphoma:** For this indication, examples of B-Cell Lymphomas were taken out of the cited indication and placed in a note. Diffuse large B-cell lymphoma was added as an example.	06/03/2020

DLBCL – Diffuse large B-cell lymphoma; NCCN – National Comprehensive Cancer Network.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Inlyta® (axitinib tablets – Pfizer)

DATE REVIEWED: 05/20/2020

OVERVIEW

Inlyta, a kinase inhibitor, is indicated for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy.[1]

Guidelines

The NCCN clinical practice guidelines on kidney cancer (version 2.2020 – August 5, 2019) recommend Inlyta + Keytruda (pembrolizumab for intravenous use) as a "preferred regimen" (category 2A) for favorable risk and poor/intermediate risk patients as first-line therapy for clear cell histology.[2] Inlyta + Imfinzi (avelumab for intravenous use) is recommended as one of the "Other recommended regimens" (category 2A) in the same populations. Inlyta as a monotherapy is a category 2B recommended regimen for first-line therapy. Inlyta is a category 1 recommended therapy under "other recommended regimens" for subsequent therapy. Inlyta + Keytruda is another category 2A option in this setting; Inlyta + Imfinzi is a category 3 option. It is one of the systemic therapy options listed under "useful under certain circumstances" for relapse or Stage IV RCC with *non-clear cell histology* (category 2A).

The NCCN thyroid carcinoma guidelines (version 2.2019 – September 16, 2019) recommend Inlyta as one of the kinase inhibitors to be considered if clinical trials or other systemic therapies are not available or appropriate for the treatment of progressive and/or symptomatic iodine refractory thyroid cancer.[3] This recommendation is for follicular, Hürthle cell, and papillary cancer subtypes (all category 2A).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Inlyta. All approvals are provided for 3 years.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Inlyta is recommended in those who meet the following criteria:

FDA-Approved Indications

65. Renal Cell Carcinoma – Clear Cell or Non-Clear Cell Histology. Approve for 3 years for relapsed or Stage IV disease.

Other Uses with Supportive Evidence

66. Differentiated (i.e., papillary, follicular, and Hürthle cell) Thyroid Carcinoma. Approve for 3 years if refractory to radioactive iodine therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Inlyta has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below.

218. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

324. Inlyta® tablets [prescribing information]. New York, NY: Pfizer Inc; January 2020.

325. The NCCN Kidney Cancer Clinical Practice Guidelines in Oncology (Version 2.2020 – August 5, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 17, 2020.
326. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (Version 2.2019 – September 16, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 17, 2020.

HISTORY

Type of Revision	Summary of Changes*	Date Reviewed
Annual revision	The Renal Cell Carcinoma criterion was revised to add predominant clear cell histology and non-clear cell histology is included. Differentiated Thyroid Carcinoma criteria were revised to only require that the patient's disease is refractory to radioactive iodine therapy. Head and Neck Cancer and Hepatocellular Carcinoma were added to the list of conditions not recommended for approval.	02/10/2016
Annual revision	Approval was removed for patient has been started on Inlyta for an indication or condition addressed as an approval in the Recommended Authorization Criteria section.	03/08/2017
Annual revision	Conditions Not Recommended for Approval: Acute Myeloid Leukemia, Breast Cancer, and Myelodysplastic Syndrome were removed.	04/11/2018
Annual revision	No criteria changes	04/24/2019
Early Annual revision	For Renal Cell Carcinoma, deleted "advanced" and "predominant" with reference to clear cell histology. Added criteria that patient has relapse or Stage IV disease. Deleted all conditions listed under Conditions Not Recommended for Approval.	05/08/2019
Annual revision	No criteria changes	05/20/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Inqovi Prior Authorization Policy

- Inqovi® (decitabine and cedazuridine tablets – Taiho Oncology/Otsuka Pharmaceutical)

REVIEW DATE: 07/22/2020

OVERVIEW

Inqovi, a combination of decitabine (a nucleoside metabolic inhibitor) and cedazuridine (a cytidine deaminase inhibitor), is indicated for the following:[1]

- **Myelodysplastic syndrome (MDS),** in adults, including previously treated and untreated, de novo and secondary MDS with the following French-American-British (FAB) subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System (IPSS) groups.

Decitabine is available as a parenteral product (Dacogen® [decitabine injection for intravenous {IV} use]; generic) and possesses the same FDA-approved indication as Inqovi.[2] The oral bioavailability of decitabine is limited due to rapid degradation by cytidine deaminase in the gut and liver.[1] As a cytidine deaminase inhibitor, cedazuridine increases decitabine concentrations to therapeutic levels. Oral decitabine has systemic exposure equivalent to the IV form with similar clinical response rates in the population in which Inqovi is FDA-approved.[1,2] The recommended dose of Inqovi is one tablet taken orally once daily on Days 1 through 5 of each 28-day cycle for a minimum of four cycles until disease progression or unacceptable toxicity. A complete or partial response may take longer than four cycles. In the two pivotal trials, the median treatment duration was up to 8 months. Do not substitute Inqovi for the IV decitabine product within a cycle.

Guidelines

Inqovi is not addressed in the guidelines. Dacogen is incorporated into the National Comprehensive Cancer Network (NCCN) guidelines for myelodysplastic syndromes (version 2.2020 – February 28, 2020) and is recommended in various clinical scenarios in patients with MDS (e.g., treatment of lower risk disease, high-risk disease) and CMML (as a single agent or with Jakafi® [ruxolitinib tablets]).[3] In Phase III studies hypomethylating agents (e.g., decitabine, Vidaza® [azacitidine injection for intravenous or subcutaneous use [generic]) have favorable data regarding hematological response and improvement, as well as a decrease in the progression to AML; survival benefits have also been noted.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Inqovi. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Inqovi is recommended in those who meet the following criteria:

FDA-Approved Indications

137. Chronic Myelomonocytic Leukemia. Approve for 1 year.

138. Myelodysplastic Syndromes. Approve for 1 year.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Inqovi is not recommended in the following situations:

149. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

277. Inqovi® tablets [prescribing information]. Princeton, NJ and Japan: Taiho Oncology, Inc. and Otsuka Pharmaceutical Co.; July 2020.
278. Dacogen® injection for intravenous use [prescribing information]. Rockville, MD and Dublin, CA: Otsuka American Pharmaceutical and Astex Pharmaceuticals; June 2020.
279. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (Version 2.2020 – February 28, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed July 14, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/22/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Inrebic Prior Authorization Policy

- Inrebic® (fedratinib capsules – Celgene)

REVIEW DATE: 08/26/2020

OVERVIEW

Inrebic, a Janus Associated Kinase 2 (JAK2)-selective kinase inhibitor, is indicated for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis. Inrebic labeling includes a Boxed Warning regarding risk of encephalopathy, including Wernicke's encephalopathy, and states that thiamine (vitamin B1) levels should be assessed prior to starting Inrebic and periodically during treatment.

Disease Overview

Myelofibrosis, polycythemia vera, and essential thrombocythemia are a group of uncommon heterogeneous disorders involving the hematopoietic system.[2-4] In the US, the prevalence of myelofibrosis, essential thrombocythemia, and polycythemia vera were approximately 13,000, 134,000, and 148,000 cases respectively.[2] It is a cancer that impacts the normal production of red blood cells and involves the replacement of bone marrow by fibrous scare tissue. There is a lack of red blood cells, and an overabundance of white blood cells. The symptom profile in myeloproliferative neoplasms is complex and symptoms vary among the subtype. Patients may experience fatigue, pruritus, weight loss, splenomegaly, and various laboratory abnormalities (e.g., erythrocytosis, thrombocytosis, and leukocytosis). The

disease can be slowly progressive and early in the disease process patients may be asymptomatic. However, some patients with this condition may have the disease transform into acute myeloid leukemia which is associated with a poor prognosis. The management of myeloproliferative neoplasms involves identification of specific mutations which guide targeted therapies and have resulted in improvement of disease symptoms. Other treatments are symptom-based.

Guidelines

The National Comprehensive Cancer Network has guidelines regarding myeloproliferative neoplasms (version 1.2020 – May 31, 2020) include Inrebic.[2] Inrebic is recommended for higher risk patients with a platelet count ≥ 10 x 10^9/L (category 2B). In this clinical scenario, Jakafi® (ruxolitinib capsules), another kinase inhibitor, has a higher recommendation (category 2A). Inrebic is also recommended in patients who have tried Jakafi with no response or who have loss of response. Jakafi is also recommended among patients with lower-risk myelofibrosis.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Inrebic. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Inrebic is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Myelofibrosis (MF), including Primary MF, Post-Polycythemia Vera MF, and Post-Essential Thrombocythemia MF.** Approve Inrebic for 3 years if the patient has intermediate-2 or high-risk disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Inrebic is not recommended in the following situations:

150. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

471. Inrebic® capsules [prescribing information]. Summit, NJ: Celgene; August 2019.
472. The NCCN Myeloproliferative Neoplasms Clinical Practice Guidelines in Oncology (Version 1.2020 – May 21, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 23, 2020.
473. Tremblay D, Marcellino B, Mascarenhas J. Pharmacotherapy of myelofibrosis. *Drugs.* 2017;77(14):1549-1563.
474. Vannucchi AM, Guglielmelli P. What are the current treatment approaches for patients with polycythemia vera and essential thrombocythemia? *Hematology Am Soc Hematol Educ Program*. 2017;2017(1):480-488.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	08/16/2019
Annual revision	No criteria changes.	08/26/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Iressa Prior Authorization Policy

- Iressa® (gefitinib tablets – AstraZeneca)

REVIEW DATE: 09/02/2020

OVERVIEW

Iressa is a tyrosine kinase inhibitor (TKI) indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (*EGFR*) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.[1] The safety and efficacy of Iressa have not been established in patients whose tumors have other *EGFR* mutations. Iressa binding affinity for *EGFR* exon 19 deletion or exon 21 point mutation L858R mutations is higher than its affinity for the wild-type *EGFR*.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for NSCLC (version 6.2020 – June 15, 2020) recommend Tarceva® (erlotinib tablets), Iressa, Gilotrif™ (afatinib tablets), Tagrisso™ (osimertinib tablets), and Vizimpro® (dacomitinib tablets) as first-line treatment in patients with sensitizing *EGFR*-mutation positive NSCLC (all category 1).[2] Tagrisso is noted as a "preferred" option. Tagrisso is the only agent specifically FDA-approved and recommended in guidelines (category 1) for T790M-positive tumors as subsequent therapy, after progression on first-line Tarceva, Iressa, Vizimpro, or Gilotrif.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Iressa. All approval durations are noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Iressa is recommended in those who meet the following criteria:

FDA-Approved Indications

67. Non-Small Cell Lung Cancer (NSCLC). Approve for 3 years if the patient meets the following criteria (A and B):
- **A)** Patient has metastatic non-small cell lung cancer; AND
- **B)** Patient meets ONE of the following conditions (i or ii):
  - **i.** Patient has epidermal growth factor receptor (*EGFR*) exon 19 deletions as detected by an approved test; OR
  - **ii.** Patient has exon 21 (L858R) substitution mutations as detected by an approved test.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Iressa is not recommended in the following situations:

219. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

280. Iressa® tablets [prescribing information]. Wilmington, DE: AstraZeneca; July 2018.

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HISTORY

Type of Revision	Summary of Changes*	Review Date
Annual revision	No criteria changes	08/15/2018
Annual revision	No criteria changes	09/11/2019
Annual revision	No criteria changes	09/02/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Jakafi Prior Authorization Policy

- Jakafi® (ruxolitinib tablets – Incyte)

REVIEW DATE: 03/25/2020

OVERVIEW

Jakafi, a kinase inhibitor, is indicated for treatment of patients with 1) intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis in adults; 2) polycythemia vera in adults who have had an inadequate response to or are intolerant of hydroxyurea; and 3) steroid-refractory acute graft-vs.-host disease in adult and pediatric patients ≥ 12 years of age.[1] Jakafi specifically inhibits Janus Associated Kinases (JAKs) JAK1 and JAK2 which mediate the signaling of various cytokinase and growth factors that are vital for hematopoiesis and immune function.

Disease Overview

Myelofibrosis, polycythemia vera, and essential thrombocythemia are a group of uncommon heterogeneous disorders involving the hematopoietic system.[2-4] In the US, the prevalence of myelofibrosis, essential thrombocythemia, and polycythemia vera were approximately 13,000, 134,000, and 148,000 cases respectively.[2] It is a cancer that impacts the normal production of red blood cells and involves the replacement of bone marrow by fibrous scare tissue. There is a lack of red blood cells, and an overabundance of white blood cells. The symptom profile in myeloproliferative neoplasms is complex and symptoms vary among the subtype. Patients may experience fatigue, pruritis, weight loss, splenomegaly, and various laboratory abnormalities (e.g., erythrocytosis, thrombocytosis, and leukocytosis). The disease can be slowly progressive and early in the disease process patients may be asymptomatic. However, some patients with this condition may have the disease transform into acute myeloid leukemia which is associated with a poor prognosis. The management of myeloproliferative neoplasms involves identification of specific mutations which guide targeted therapies and have resulted in improvement of disease symptoms. Other treatment are symptom-based.

Guidelines

The National Comprehensive Cancer Network (NCCN) has guidelines regarding myeloproliferative neoplasms (version 3.2019 – September 4, 2019) that include Jakafi.[2] Jakafi is recommended among patients with low-, intermediate-, and high-risk myelofibrosis. It is also a recommended therapy for patients with high-risk polycythemia vera.

The NCCN has guidelines regarding hematopoietic cell transplantation that discuss graft-versus-host disease (version 1.2020 – October 30, 2019) that include Jakafi.[7] Jakafi is recommended among patients with steroid-refractory chronic graft-vs.-host disease.[7] Supportive data are available.[8,9] A variety of other agents are also recommended such as cyclosporine, tacrolimus, mycophenolate mofetil, Imbruvica® (ibrutinib capsules and tablets), and imatinib.

The NCCN guidelines for pediatric acute lymphoblastic leukemia (ALL) [version 2.2020 – November 25, 2019] recommend Jakafi in a variety of regimens for pediatric patients and young adults with ALL.[10] The utility of Jakafi is described primarily in patients in which the mutation/pathway is Janus Associated Kinase (JAK)-related.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Jakafi. All approvals are provided for the durations noted below.

Automation: The ICD-9/ICD-10 codes for myelofibrosis (ICD-9: 289.83 and ICD-10: D75.81) will be used as part of automation to allow approval of the requested medication.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Jakafi is recommended in those who meet the following criteria:

FDA-Approved Indications

68. Graft versus Host Disease, Acute. Approve for 1 year if the patient has tried one systemic corticosteroid.

69. Myelofibrosis (MF), including Primary MF, Post-Polycythemia Vera MF, and Post-Essential Thrombocythemia MF. Approve for 3 years.

70. Polycythemia Vera. Approve for 3 years if the patient has tried hydroxyurea.

Other Uses with Supportive Evidence

71. Acute Lymphoblastic Leukemia. Approve for 1 year if the patient meets the following criteria (A and B)
- **A)** The patient is < 21 years of age; AND
- **B)** The mutation/pathway is Janus Associated Kinase (JAK)-related.

72. Graft versus Host Disease, Chronic. Approve for 1 year if the patient has tried one conventional systemic treatment for graft versus host disease.

Note: Examples include systemic corticosteroids [methylprednisolone, prednisone], cyclosporine, tacrolimus, mycophenolate mofetil, Imbruvica® (ibrutinib capsules and tablets), and imatinib.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Jakafi has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

220. Other Refractory Leukemias. Limited data have investigated Jakafi in adults with relapsed and/or refractory acute myeloid leukemia (AML), myelodysplastic syndromes (MDS) [including chronic myelomonocytic leukemia {CMML}], or chronic myelocytic leukemia (CML).[5,6] Further studies are needed to determine the place in therapy of Jakafi for the treatment of refractory leukemias.

221. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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336. The NCCN Pediatric Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (Version 2.2020 – November 25, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 9, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes	02/14/2018
Annual Revision	No criteria changes	02/27/2019
Selected Revision	Graft Versus Host Disease, Acute: Approval criteria were added for this diagnosis if the patient has tried one systemic corticosteroid.	06/05/2019
Annual Revision	The following indications were added: **1.** Graft-Versus-Host Disease, Chronic: Criteria were added under the Other Uses with Supportive Evidence section, to approve for 1 year if the patient has tried one conventional system treatment for graft vs. host disease. Examples of agents were provided in a note. **2.** Acute Lymphoblastic Leukemia. Criteria were added under the Other Uses with Supportive Evidence section to approve for 1 year if the patient is < 21 years of age and the mutation/pathway is Janus Associated Kinase-related.	03/25/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Kisqali and Kisqali Femara Co-Pack Prior Authorization Policy
- Kisqali® (ribociclib tablets – Pfizer)
- Kisqali® Femara® Co-Pack (ribociclib tablets; letrozole tablets, co-packaged for oral use – Pfizer)

REVIEW DATE: 02/24/2021

OVERVIEW

Kisqali, a cyclin-dependent kinase (CDK) 4/6 inhibitor, is indicated in hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative **advanced or metastatic breast cancer** in the following settings:[1-3]

- In combination with an aromatase inhibitor (AI) as initial endocrine-based therapy for the treatment of pre/perimenopausal or postmenopausal women with.
- Kisqali (not Co-Pack) in combination with fulvestrant for the treatment of postmenopausal women, as initial endocrine based therapy or following disease progression on endocrine therapy.
- Kisqali Femara Co-Pack has the same indication with the aromatase inhibitor, letrozole being provided.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on breast cancer (version 1.2021 – January 15, 2021) recommend any of the CDK4/6 inhibitors in combination with an AI or fulvestrant as a first-line preferred treatment option for recurrent or Stage IV HR+ and HER2-negative disease in postmenopausal women or premenopausal patient receiving ovarian ablation or suppression (category 1).[3,4] CDK4/6 inhibitor + fulvestrant is recommended for second- and subsequent-line therapy, if CDK4/6 inhibitor was not previously used (category 1). However, the guidelines also state in a footnote that if there is disease progression on CDK4/6 inhibitor therapy or PI3K inhibitor, there are limited data to support an additional line of therapy with another CDK4/6-containing regimen.[3,5] For men with breast cancer, the compendium recommends they be treated similarly to postmenopausal women, except that the use of an AI is ineffective without concomitant suppression of testicular steroidogenesis.[4]

Supportive Data

A multicenter analysis evaluated clinical outcomes in patients (n = 58) with HR+/HER2-negative metastatic breast cancer who received Verzenio (abemaciclib tablets) after disease progression on Ibrance (palbociclib tablets) or Kisqali.[5] At data cutoff, 34% of patients (n = 20/58) had progressive disease, while 36% of patients (n = 21/58) had treatment duration exceeding 6 months. The median progression-free survival (PFS) was 5.8 months. Another case report of Verzenio use after 10 lines of therapy, including Ibrance therapy is available, along with literature review of ongoing studies with other CDK 4/6 inhibitors after prior use of another inhibitor.[6] Ibrance and Kisqali also have ongoing studies assessing for their respective efficacy after progression on another CDK4/6 inhibitor.[7,8] Preliminary results from the Kisqali trial (TRINITI-1), a Phase I/II, open-label trial of triplet therapy (Kisqali + everolimus + exemestane) after progression on prior CDK 4/6 inhibitor and up to three lines of therapy are available.[9] A total of 95 patients were evaluated; 41.1% of patients demonstrated clinical benefit, exceeding the predefined primary endpoint threshold (> 10%). The response rate was 8.4% and the median PFS was 5.7 months, and the 1-year PFS was 33%.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Kisqali and Kisqali Femara Co-Pack. All approvals are provided for 3 years in duration unless otherwise noted below. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: a woman is defined as an individual with the biological traits of a woman, regardless of the individual's gender identity or gender expression; men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Kisqali is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Breast Cancer in Postmenopausal Women***. Approve for 3 years if the patient meets the following criteria (A, B, and C):
   - **10.** Patient has advanced or metastatic hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND
   - **11.** Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
   - **12.** Patient meets ONE of the following criteria (i or ii):
     - **i.** Kisqali will be used in combination with anastrozole, exemestane, or letrozole; OR
     - **ii.** Kisqali will be used in combination with fulvestrant.

   ***** Refer to the Policy Statement.

2. **Breast Cancer in Pre/Perimenopausal Women*.** Approve for 3 years if the patient meets the following criteria (A, B, C, and D):
   - **A)** Patient has advanced or metastatic hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND
   - **B)** Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
   - **C)** Patient is receiving ovarian suppression/ablation with a gonadotropin-releasing hormone (GnRH) agonist or has had surgical bilateral oophorectomy or ovarian irradiation; AND
     Note: Examples of GnRH agonists are Lupron (leuprolide), Trelstar (triptorelin), Zoladex (goserelin).
   - **D)** Patient meets one of the following criteria (i or ii):
     - **i.** Kisqali will be used in combination with anastrozole, exemestane, or letrozole; OR
     - **ii.** Kisqali will be used in combination with fulvestrant**.**

   ***** Refer to the Policy Statement.

Other Uses with Supportive Evidence

3. **Breast Cancer in Men*.** Approve for 3 years if the patient meets the following criteria (A, B, C, and D):
   - **A)** Patient has advanced or metastatic hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND
   - **B)** Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
   - **C)** Patient meets ONE of the following criteria (i or ii):
     - **i.** Patient meets BOTH of the following criteria (a and b):
       - **a)** Patient is receiving a gonadotropin-releasing hormone (GnRH) analog; AND

Note: Examples are Lupron (leuprolide), Trelstar (triptorelin), Zoladex (goserelin], Firmagon (degarelix), Orgovyx (relugolix).

b) Kisqali will be used in combination with anastrozole, exemestane, or letrozole; OR

ii. Kisqali will be used in combination with fulvestrant.

***** Refer to the Policy Statement.

II. Coverage of Kisqali Femara Co-Pack is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Breast Cancer in Women***. Approve for 3 years if the patient meets the following criteria (A, B, and C):
   2. Patient has advanced or metastatic hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND
   ~~3.~~**2.** Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
   ~~4.~~**2.** If the patient is premenopausal or perimenopausal, then the patient is receiving ovarian suppression/ablation with a gonadotropin-releasing hormone (GnRH) agonist or has had surgical bilateral oophorectomy or ovarian irradiation.
   Note: Examples of GnRH agonists are Lupron (leuprolide), Trelstar (triptorelin), Zoladex (goserelin).

   ***** Refer to the Policy Statement.

Other Uses with Supportive Evidence

1. **Breast Cancer in Men*.** Approve for 3 years if the patient meets the following criteria (A, B, and C):
   A) Patient has advanced or metastatic hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND
   B) Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
   C) Patient is receiving a gonadotropin-releasing hormone (GnRH) analog.
   Note: Examples are Lupron [leuprolide], Trelstar [triptorelin], Zoladex (goserelin), Firmagon (degarelix), Orgovyx (relugolix).

   ***** Refer to the Policy Statement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kisqali or Kisqali Femara Co-Pack is not recommended in the following situations:

222. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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History

Type of Revision	Summary of Changes	Review Date
Annual Revision	Deleted criteria in all indications requiring Kisqali + aromatase inhibitors to be used as "first-line (initial) endocrine therapy". Now the combination can be used in any setting. Kisqali + Faslodex use was added to premenopausal women based on guidelines. For Kisqali + Faslodex use in postmenopausal women and men indications, deleted criteria requiring prior endocrine therapy use or that it be used as first-line endocrine therapy. For Kisqali Femara Co-Pack since approval is in "women" (includes postmenopausal and premenopausal), deleted specific reference to postmenopausal patient. Instead re-phrased to state, "If patient is premenopausal or perimenopausal…" then patient is receiving ovarian suppression/ablation. For premenopausal patients, added criteria that Kisqali can be used in combination with tamoxifen based on guidelines.	04/03/2019
Annual Revision	Criteria for Kisqali use in combination with tamoxifen as first-line therapy has been deleted for pre/perimenopausal women since it is no longer supported in guidelines due to QTc prolongation.	04/15/2020
Early Annual Revision	**All Breast Cancer Indications:** For Kisqali and Kisqali Femara Co-Pack deleted criteria requiring no disease progression on Kisqali, Ibrance (palbociclib) or Verzenio (abemaciclib), based on guidelines and available data. **Breast Cancer in Pre/Perimenopausal Women:** Examples of gonadotropin-releasing hormone (GnRH) agonists are moved from criteria to Note. **Breast Cancer in Men:** For this indication in Kisqali and Kisqali Femara Co-pack, GnRH "agonist" is changed to "analog". Also, the list of examples of GnRH analog agents are moved from criteria to Note. Firmagon (degarelix) and Orgovyx (relugolix) were added to example list. **Breast Cancer in Women:** Examples of gonadotropin- releasing hormone (GnRH) agonists are moved from criteria to Note.	02/24/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Koselugo™ (selumetinib capsules – AstraZeneca Pharmaceuticals)

DATE REVIEWED: 04/15/2020

OVERVIEW

Koselugo (selumetinib), a kinase inhibitor, is indicated for the treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas.[1]

Koselugo is a mitogen-activated protein kinase kinases 1 and 2 (MEK1/2) inhibitor.[1]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Koselugo. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Koselugo is recommended in those who meet the following criteria:

FDA-Approved Indications

139. Neurofibromatosis Type 1. Approve for 3 years if the patient meets the following criteria (A and B):

A) The patient meets ONE of the following (i or ii):
- **i.** Patient is 2 to 18 years of age; OR
- **ii.** Patient is ≥ 19 years of age AND has been previously started on therapy with Koselugo prior to becoming 19 years of age; AND

B) Prior to starting Koselugo, the patient has symptomatic, inoperable plexiform neurofibromas, according to the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Koselugo has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

151. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

475. Koselugo™ capsules [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals; April 2020.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Lapatinib (Tykerb) Prior Authorization Policy

- Tykerb® (lapatinib ditosylate tablets – Novartis Pharmaceuticals; generics)

OVERVIEW

Lapatinib, a tyrosine kinase inhibitor, is indicated for the following uses:[1]

- **Breast cancer**, in combination with capecitabine tablets for the treatment of patients with **advanced or metastatic disease** whose tumors overexpress human epidermal growth factor receptor 2 (HER2) and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.
  Limitation of use. Patients should have disease progression on trastuzumab prior to initiation of treatment with lapatinib in combination with capecitabine tablets.
- **Breast cancer**, in combination with letrozole tablets for the treatment of postmenopausal women with **hormone receptor-positive (HR+) metastatic disease** that overexpresses HER2 for whom hormonal therapy is indicated. Lapatinib in combination with an aromatase inhibitor (AI) has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer.

Guidelines

- **Breast Cancer:** The National Comprehensive Cancer Network (NCCN) clinical practice guidelines on breast cancer (version 6.2020 – September 8, 2020) recommend laptinib in combination with trastuzumab (without cytotoxic therapy) or capecitabine for HER2-positive (HER2+) recurrent or metastatic trastuzumab-exposed disease with symptomatic visceral disease or visceral crisis OR that is hormone receptor-negative or HR+ and endocrine therapy refractory (category 2A).[2] Lapatinib is also recommended in combination with an AI with or without trastuzumab for the treatment of recurrent or Stage IV HR+, HER2+ disease in postmenopausal women.[2] Premenopausal women with HR+ disease should have ovarian ablation/suppression and follow the guidelines for postmenopausal patients. Men with breast cancer should be treated similarly to postmenopausal women except that using an AI is ineffective without suppression of testicular steroidogenesis (category 2A). The NCCN clinical practice guidelines on central nervous system (CNS) cancers (version 3.2020 – September 11, 2020) recommend treatments for patients with brain metastases from breast cancer.[3,4] Capecitabine with or without lapatinib is recommended for recurrent disease in patients with limited (one to three) metastatic lesions or treatment for recurrent stable systemic disease in patients with multiple (> three) metastatic lesions if lapatinib is active against the primary tumor (breast).
- **Bone Cancer:** The NCCN guidelines for bone cancer (version 1.2021 – November 20, 2020) and the compendium recommends the use of lapatinib for epidermal growth factor receptor (*EGFR)*-positive recurrent disease.[3,5]
- **Colon or Rectal Cancer:** The NCCN Compendium supports the use of lapatinib in colon or rectal cancer for HER2-amplified, RAS and BRAF wild-type disease, in combination with trastuzumab.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tykerb. All approvals are provided for 3 years in duration unless otherwise noted below. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: a woman is defined as an individual with the biological traits of a woman, regardless of the individual's gender identity or gender expression; a man is defined as an individual with the biological traits of a man, regardless of the individual's gender identity or expression.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of lapatinib is recommended in those who meet the following criteria:

FDA-Approved Indications

16. Breast Cancer, Human Epidermal Growth Factor Receptor 2 Positive (HER2+). Approve for 3 years if the patient meets one of the following criteria (A or B):

- **A)** Patient has advanced or metastatic breast cancer and the following criteria are met (i or ii):
  - **i.** Patient has received prior therapy with trastuzumab AND the medication will be used in combination with capecitabine; OR
  - **ii.** The medication will be used in combination with trastuzumab; OR
- **B)** Patient has hormone receptor-positive (that is, estrogen- and/or progesterone-positive) metastatic breast cancer and the following criteria are met (i and ii):
  - **i.** One of the following (a, b, or c) applies:
    - **a)** Patient is a postmenopausal woman*; OR
    - **b)** Patient is a premenopausal or perimenopausal woman* and is receiving ovarian suppression/ablation with a gonadotropin-releasing hormone (GnRH) agonist, surgical bilateral oophorectomy, or ovarian irradiation; OR
      Note: Examples are Lupron® [leuprolide], Trelstar® [triptorelin], Zoladex® (goserelin].
    - **c)** Patient is a man* and is receiving a gonadotropin-releasing hormone (GnRH) agonist; AND
      Note: Examples are Lupron [leuprolide, Trelstar [triptorelin], Zoladex (goserelin].
  - **ii.** The medication will be used in combination with an aromatase inhibitor (that is, letrozole, anastrozole, or exemestane).

***** Refer to the Policy Statement.

Other Uses with Supportive Evidence

2. Bone Cancer – Chordoma. Approve for 3 years if the patient has epidermal growth-factor receptor (*EGFR*)-positive recurrent disease.

3. Colon or Rectal Cancer. Approve for 3 years if the patient meets the following criteria (A, B, and C):

- **A)** Patient has unresectable advanced or metastatic disease that is human epidermal receptor2 (HER2)-amplified and with wild-type RAS; AND
- **B)** The medication is used as subsequent therapy in combination with trastuzumab; AND
- **C)** Patient has not been previously treated with a HER2-inhibitor.
  Note: Examples of HER2-inhibitors are trastuzumab products, Nerlynx (neratinib tablets), Kadcyla (ado-trastuzumab emtansine for injection), Perjeta (pertuzumab for injection).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of lapatinib is not recommended in the following situations:

223. **Cervical Cancer.** In one Phase II study (n = 228), Tykerb plus Votrient® (pazopanib tablets) was compared with lapatinib monotherapy or Votrient monotherapy in patients with advanced and recurrent cervical cancer.[6] At the interim analysis, the futility boundary was crossed for combination therapy vs. lapatinib monotherapy, and the combinati○on arm was discontinued. The median PFS was shorter among lapatinib-treated patients vs. Votrient-treated patients (17.1 weeks vs. 18.1 weeks, respectively; HR 0.66; 90% CI: 0.48, 0.91; P < 0.013). On the clinical cutoff date, median OS was 11.6 weeks greater with Votrient vs. lapatinib (50.7 weeks vs. 39.1 weeks; HR: 0.67; 90% CI: 0.46, 0.99; P = 0.045). Patients were not preselected on the basis of EGFR or HER2 amplification.

224. **Gastric, Esophageal, or Gastroesophageal Adenocarcinoma Cancer.** In one Phase II study (n = 47), lapatinib demonstrated modest activity in patients with treatment-naïve advanced/metastatic gastric cancer.[7] A total of four patients had a confirmed partial response, one patient had an unconfirmed partial response, and 10 patients had stable disease. An exploratory analysis revealed gene expression of HER2, interleukin (IL)-8 and genomic polymorphisms IL-8, and vascular endothelial growth factor (VEGF) correlated with OS. In one Phase III, open-label trial conducted in China, Japan, South Korea, and Taiwan, Asian patients (n = 261) with HER2+ advanced gastric cancer were randomized to lapatinib 1,500 mg per day plus paclitaxel 80 mg/m^2 on Days 1, 8, and 15 of a 28-day cycle or to paclitaxel alone.[8] Patients had disease progression after prior therapy. The primary endpoint was OS. Median OS was 11.0 months in patients receiving lapatinib plus paclitaxel vs. 8.9 months with paclitaxel alone (P = 0.1044). There was no significant difference between lapatinib plus paclitaxel or paclitaxel alone in median PFS (5.4 vs. 4.4 months) or time to progression (5.5 vs. 4.4 months), respectively. Overall response rate (ORR) was higher with lapatinib plus paclitaxel vs. paclitaxel alone (27% vs. 9%, respectively; 95% CI: 1.80, 8.87; P <0.001). In one Phase III trial in patients (n = 545) with previously untreated HER2+ advanced gastroesophageal adenocarcinoma were randomized to receive CapeOx (capecitabine plus oxaliplatin) with either lapatinib or placebo.[9] Median OS was 12.2 months (95% CI: 10.6, 14.2) and 10.5 months (95% CI: 9.0, 11.3) for lapatinib and placebo, respectively (HR 0.91; 95% CI: 0.73, 1.12). Preplanned exploratory analysis showed OS in the lapatinib was prolonged in Asian and younger patients.

225. **Head and Neck, Squamous Cell Carcinoma.** In one Phase III study in 688 patients with SCCHN, adding lapatinib to chemoradiotherapy and as maintenance monotherapy was not more effective than placebo in improving disease-free survival or OS.[10]

226. **Renal Cell Carcinoma (RCC).** In one Phase III study in patients (n = 416) with advanced RCC who experienced disease progression through first-line cytokine therapy, lapatinib and hormone therapy (megestrol acetate or tamoxifen, selected by the investigator) demonstrated comparable efficacy: the median time to progression was 15.3 weeks and 15.4 weeks for lapatinib and hormone therapy, respectively (HR 0.94; P = 0.60).[11] The median OS was 46.9 weeks and 43.1 weeks for lapatinib and hormone therapy, respectively (HR 0.88; P = 0.29).

227. **Urothelial Carcinoma.** In one Phase III trial, 232 patients with HER1/HER2 metastatic urothelial bladder cancer who did not have progressive disease during chemotherapy were randomized to receive lapatinib or placebo after completing first-line or initial chemotherapy.[12] Median PFS, the primary endpoint, for lapatinib and placebo was 4.5 months (95% CI: 2.8, 5.4) and 5.1 months (95% CI: 3.0, 5.8), respectively (HR 1.07; 95% CI: 0.81, 1.43; P = 0.63).

228. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Tykerb® tablets [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; September 2018.
2. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 6.2020 – September 8, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 11, 2021.
3. The NCCN Drugs & Biologics Compendium. © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 10, 2021. Search terms: lapatinib.
4. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 3.2020 – September 11, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http:/www.nccn.org. Accessed on January 14, 2021.
5. The NCCN Bone Cancer Clinical Practice Guidelines in Oncology (version 1.2021 – November 20, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 14, 2021.
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9. Hecht JR, Bang YJ, Qin SK, et al. Lapatinib in combination with capecitabine plus oxaliplatin in human epidermal growth factor receptor 2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma: TRIO-013/LOGiC-a randomized phase III trial. *J Clin Oncol*. 2016;34:443-451
10. Harrington K, Temam S, Mehanna H, et al. Postoperative adjuvant lapatinib and concurrent chemoradiotherapy followed by maintenance lapatinib monotherapy in high-risk patients with resected squamous cell carcinoma of the head and neck: A phase III, randomized, double-blind, placebo-controlled study. *J Clin Oncol*. 2015;33:4202-4209.
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12. Powles T, Huddart RA, Elliott T, et al. Phase III, couble-blind, randomized trial that compared maintenance lapatinib versus placebo after first-line chemotherapy in patients with human epidermal growth factor receptor 1/2-positive metastatic bladder cancer. *J Clin Oncol*. 2017;35(1):48-55.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Added new condition for approval in Chordoma based on guidelines/compendium.	12/20/2018
Annual Revision	For Breast Cancer, rearranged criteria to state Tykerb + capecitabine can be used if patient has previously tried trastuzumab. Added new condition of approval under Other Uses with Supportive Evidence for Colon or Rectal cancer based on guidelines. Under Conditions Not Recommended for Approval, deleted the following conditions: Adenoid/non-adenoid cystic carcinoma of the salivary gland, biliary cancer, glioblastoma multiforme, hepatocellular carcinoma, non-small cell lung cancer, ovarian or peritoneal cancer, and prostate cancer.	12/18/2019
Annual Revision	• Tykerb is available as generics; changed Tykerb in filename to generic name. Also changed to generic throughout document where applicable • **Breast Cancer, Human Epidermal Growth Factor Receptor 2 Positive (HER2+):** Moved examples of GnRH agonist from criteria to Note.	01/13/2021

HR+ -- Hormone receptor positive; HER2 – Human epidermal growth factor receptor 2; LHRH – Luteinizing hormone-releasing hormone; GnRH – Gonadotropin-releasing hormone.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Lenvima™ (lenvatinib capsules – Eisai)

DATE REVIEWED: 05/13/2020

OVERVIEW

Lenvima, a kinase inhibitor, is indicated for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC).[1] Lenvima is also indicated, in combination with Afinitor® (everolimus tablets), for the treatment of patients with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy. In addition, it is also indicated for the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC). Lenvima, in combination with Keytruda (pembrolizumab for injection), is indicated for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation. This indication is approved under accelerated approval based on tumor response rate and durability of response.

Guidelines

According to the National Comprehensive Cancer Network (NCCN) guidelines on thyroid carcinoma (version 2.2019 – September 16, 2019), first-line treatment for DTC is surgery, whenever possible, followed by RAI therapy in selected patients, and levothyroxine therapy in all patients.[2] Systemic therapy options include cytotoxic chemotherapy and kinase inhibitors. Multitargeted kinase inhibitors are recommended in current guidelines for select patients with DTC. The guidelines state that for progressive and/or symptomatic disease, Lenvima (preferred) or Nexavar® (sorafenib tablets) should be considered (Category 2A). It is noted that the majority of the NCCN panel considered Lenvima to be preferred agent in this patient population based on the response rate observed in clinical trials. Lenvima can be considered for treatment of progressive or symptomatic medullary thyroid disease if clinical trials, Caprelsa, or Cometriq are not available or appropriate, or if there is progression on Caprelsa or Cometriq.[2] Lenvima is also listed as "useful under certain circumstances" for anaplastic thyroid carcinoma if there is no curative option and if the patient is not tolerating or has no response to recommended therapies.[4] The compendium notes that Lenvima can be used either first-line for aggressive metastatic disease or as subsequent therapy.

The NCCN kidney cancer guidelines (version 2.2020 – August 5, 2019) recommends Lenvima + everolimus as one of the "other recommended regimens" (category 1) for relapse or stage IV subsequent therapy for clear cell histology. It is also a recommended combination therapy (category 2A) listed as "useful under certain circumstances" for non-clear cell histology.

The NCCN hepatobiliary cancers (version 2.2020 – May 8, 2020) recommends Lenvima as preferred first-line systemic therapy (Child-Pugh Class A only) for hepatocellular carcinoma. It is also recommended as subsequent-line therapy upon disease progression (category 2A).

The NCCN uterine neoplasms guidelines (version 1.2020 – March 6, 2020) recommends Lenvima with Keytruda combination therapy for recurrent, metastatic, or high-risk endometrial carcinoma. This combination is a category 2A recommendation under "Other Recommended Regimens".

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Lenvima. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lenvima is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Differentiated (i.e., Papillary, Follicular, and Hürthle) Thyroid Carcinoma.** Approve for 3 years if the disease is refractory to radioactive iodine therapy.

2. **Renal Cell Carcinoma (Clear Cell or Non-Clear Cell).** Approve for 3 years if the patient meets the following criteria (A, B, and C):
   - **A)** The patient has relapsed or Stage IV disease; AND
   - **B)** If disease is predominant clear-cell histology, then the patient has tried one antiangiogenic therapy. Note: Examples are Inlyta® [axitinib tablets], Votrient® [pazopanib tablets], Sutent® [sunitinib capsules], or Cabometyx® [cabozantinib tablets]; AND
   - **C)** Lenvima is used in combination with everolimus /Afinitor® Disperz™ (everolimus tablets for oral suspension) therapy.

3. **Hepatocellular Carcinoma, Unresectable.** Approve for 3 years.

4. **Endometrial Carcinoma.** Approve for 3 years if the patient meets the following criteria (A, B, C, and D):
   - **A)** The patient has advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND
   - **B)** The medication is used in combination with Keytruda (pembrolizumab for intravenous injection); AND
   - **C)** The disease has progressed on at least one prior systemic therapy. Note: Examples of systemic therapy are carboplatin, paclitaxel, docetaxel, cisplatin, doxorubicin, ifosfamide, everolimus, letrozole; AND
   - **D)** The patient is not a candidate for curative surgery or radiation.

Other Uses with Supportive Evidence

5. **Medullary Thyroid Carcinoma.** Approve for 3 years if the patient has tried Caprelsa (vandetanib tablets) or Cometriq (cabozantinib capsules).

6. **Anaplastic Thyroid Carcinoma.** Approve for 3 years if the disease does not have a curative option.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Lenvima has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

229. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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2. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (Version 2.2019 – September 16, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 11, 2020.
3. The NCCN Kidney Cancer Clinical Practice Guidelines in Oncology (Version 2.2020 – August 5, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 11, 2020.
4. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 11, 2020. Search term: lenvatinib.
5. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (Version 1.2020 – March 6, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 11, 2020.
6. The NCCN Hepatobiliary Cancers Clinical Practice Guidelines in Oncology (Version 2.2020 – May 8, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 11, 2020.

History

Type of Revision	Summary of Changes*	Date Reviewed
Annual revision	Deleted Hepatocellular Carcinoma from Conditions Not Recommended for Approval due to pending positive Phase III data results. Also deleted Melanoma from the same section.	03/15/2017
Annual revision	For Renal Cell Carcinoma indication, deleted "Nexavar" from list of examples and added "Cabometyx" instead, based on guidelines. Deleted Medullary Thyroid Carcinoma from Conditional Not Recommended for Approval and moved it to approval conditions under Other Uses with Supportive Evidence, based on thyroid carcinoma guidelines/compendium. Added Hepatocellular Carcinoma as an approval condition under Other Uses based on the published Phase III study comparing it with Nexavar. Deleted Endometrial Cancer and Non-Small Cell Lung Cancer from Conditions Not Recommended for Approval due to lack of new data.	04/11/2018
Selected revision	Moved Hepatocellular Cancer to FDA-approved indications. Added qualifier "First-Line Treatment" based on approved indication.	09/05/2018
Annual revision	Added qualifier "(Clear Cell or Non-Clear Cell)" to renal cell carcinoma indication. Deleted "advanced" from condition qualifier; instead added criteria the patient has relapsed or stage IV disease as per guidelines. Deleted separate criteria for clear cell and non-clear cell; instead noted that "if disease is predominant clear cell histology" then patient has tried prior therapy. Added approval for anaplastic thyroid carcinoma if the disease does not have curative option based on guidelines/compendium.	04/17/2019
Selected revision	Added new approval condition for endometrial carcinoma based on FDA approval.	10/09/2019
Annual revision	For Hepatocellular Carcinoma indication, deleted"First-Line Treatment", since the guidelines recommend Lenvima for subsequent therapy as well.	05/13/2020

NCCN – National Comprehensive Cancer Network; NA – Not applicable; RCC – Renal cell carcinoma.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Lonsurf® (trifluridine and tipiracil tablets – Taiho Oncology Inc)

DATE REVIEWED: 02/26/2020

OVERVIEW

Lonsurf is a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor, indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor (VEGF) biological therapy, and if *RAS* wild-type, an anti-epidermal growth factor receptor (EGFR) therapy.[1] Fluoropyrimidines include 5-fluorouracil (5-FU) intravenous (IV) injection and capecitabine tablets. Anti-VEGF therapies for mCRC include Avastin® (bevacizumab solution for IV injection) and Cyramza® (ramucirumab injection for IV use). Anti-EGFR therapies for mCRC include Erbitux® (cetuximab injection for IV infusion) and Vectibix® (panitumumab injection for IV infusion).

Lonsurf is indicated for the treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, human epidermal growth factor receptor 2 (HER2)/neu-targeted therapy.[1]

Guidelines

Colon and/or Rectal Cancer

The National Comprehensive Cancer Network (NCCN) colon cancer (version 1.2020 – December, 19, 2019) and rectal cancer (version 1.2020 – December 19, 2019) guidelines recommend Lonsurf as subsequent therapy as a single agent for unresectable advanced or metastatic disease not previously treated with Lonsurf for the following uses:[2-3] for first progression (*KRAS/NRAS* mutant only) or second progression for disease previously treated with FOLFOXIRI (5-FU/leucovorin, irinotecan, oxaliplatin) with or without Avastin, for second progression for disease previously treated with irinotecan- and oxaliplatin-based regimens, or for progression for disease that progressed through all available regimens, including Stivarga® (regorafenib tablets). Lonsurf may be given before or after Stivarga.

Gastric Cancer and/or Esophageal and Esophagogastric Junction Cancer

The NCCN gastric cancer (version 4.2019 – December 20, 2019), and the esophageal and esophagogastric cancer (version 4.2019 – December 20, 2019) guidelines recommend Lonsurf as a single agent for the third line or subsequent therapy for unresectable locally advanced, recurrent, or metastatic gastric and esophagogastric junction adenocarcinoma following prior fluoropyrimidine-, platinum-, taxane-, or irinotecan-based chemotherapy.[4-6]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Lonsurf. All approvals are provided for 3 years in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lonsurf is recommended in those who meet the following criteria:

FDA-Approved Indications

~~5.~~2. **Colon and Rectal Cancer.** Approve for 3 years if the patient meets the following criteria (A, B, C, and D):[1]

- **A)** The patient has been previously treated with a fluoropyrimidine (e.g., capecitabine, 5-fluorouracil [5-FU]); AND
- **B)** The patient has been previously treated with oxaliplatin; AND
- **C)** The patient has been previously treated with irinotecan; AND
- **D)** If the patient's tumor or metastases are wild-type *RAS* (*KRAS* wild-type and/or *NRAS* wild-type) [that is, the tumors or metastases are *KRAS* and/or *NRAS* mutation negative], Erbitux (cetuximab injection for intravenous infusion) or Vectibix (panitumumab injection for intravenous infusion) has been tried.

2. **Gastric or Gastroesophageal Junction Adenocarcinoma.** Approve for 3 years if the patient has been previously treated with at least two chemotherapy regimens for gastric or gastroesophageal junction adenocarcinoma (e.g., regimens containing one or more of the following agents: capecitabine, 5-fluorouracil [5-FU]), oxaliplatin. paclitaxel, docetaxel, and irinotecan).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Lonsurf has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

230. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

291. Lonsurf® tablets [prescribing information]. Princeton, NJ: Taiho Oncology Inc.; February 2019.
292. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 1.2020 – December 19, 2019). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on: February 17, 2020.
293. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (Version 1.2020 – December 19, 2019). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on: February 17, 2020.
294. The NCCN Gastric Cancer Clinical Practice Guidelines in Oncology (Version 4.2019 – December 20, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on: February 17, 2020.
295. The NCCN Esophageal and Esophagogastric Junction Cancers Clinical Practice Guidelines in Oncology (Version 4.2019 – December 20, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on: February 17, 2019.
296. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 17, 2020. Search term: trifluridine/tipiracil.

HISTORY

Type of Revision	Summary of Changes*	Date Reviewed
Annual	Colorectal Cancer criteria revised to add wild-type *RAS*. Previously criteria stated *KRAS* and/or *NRAS* that are the components of *RAS*. Wild-type refers to both *KRAS* and *NRAS*.	10/25/2017
Annual	Removed criteria for patient already started on Lonsurf	10/17/2018
Early annual revision	Added gastric and gastroesophageal junction adenocarcinoma, metastatic as a new condition of approval.	03/06/2019
Annual	Colon and rectal cancer: Removed metastatic from indication for approval. Gastric and gastroesophageal junction adenocarcinoma: Removed metastatic from indication for approval.	02/26/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Lorbrena Prior Authorization Policy
- Lorbrena® (lorlatinib tablets – Pfizer)

REVIEW DATE: 11/18/2020; selected revision 03/17/2021

OVERVIEW
Lorbrena, a kinase inhibitor, is indicated for the treatment of adult patients with **anaplastic lymphoma kinase (*ALK*)-positive metastatic non-small cell lung cancer (NSCLC)** as detected by an FDA-approved test.[1]

GUIDELINES
According to the National Comprehensive Cancer Network (NCCN) NSCLC guidelines (version 4.2021 – March 3, 2021), Alecensa® (alectinib capsules), Alunbrig™ (brigatinib tablets), and Lorbrena are all category 1, first-line,preferred regimens.[2] Other category 1 recommended regimen is Zykadia® (ceritinib capsules). Xalkori is listed as useful in certain circumstances, but it's also a category 1 option. Lorbrena is also recommended as subsequent therapy upon progression on Alecensa, Alunbrig, or Zykadia (category 2A). If Xalkori is used first-line, then Lorbrena is used for subsequent therapy after progression on Alecensa, Alunbrig, or Zykadia (category 2A). Lorbrena is also recommended as subsequent therapy after progression on Xalkori, Rozlytrek (entrectinib capsules) [both "Preferred"], or Zykadia [all category 2A] for ROS1 rearrangement-positive NSCLC. Zykadia is listed as "other recommended" agent in the first-line setting for ROS1 rearrangement.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Lorbrena. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Lorbrena is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Non-Small Cell Lung Cancer (NSCLC).** Approve for 3 years if the patient meets the following criteria (A and B):

A) Patient is ≥ 18 years of age; AND
B) Patient has anaplastic lymphoma kinase (*ALK*)-positive metastatic NSCLC, as detected by an approved test.

Other uses With Supportive Evidence

2. Non-Small Cell Lung Cancer. Approve for 3 years if the patient meets the following criteria (A, B, and C):
A) Patient is ≥ 18 years of age; AND
B) Patient has *ROS1* rearrangement-positive disease; AND
C) Patient has tried at least one of Xalkori (crizotinib capsules), Zykadia (ceritinib capsules), or Rozlytrek (entrectinib capsules).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lorbrena is not recommended in the following situations:

231. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

337. Lorbrena® tablets [prescribing information]. New York, NY: Pfizer; March 2021.
338. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 4.2021 – March 3, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 16, 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	11/7/2018
Annual Revision	Added new approval condition for ROS1-positive non-small cell lung cancer.	11/13/2019
Annual Revision	**Non-Small Cell Lung Cancer:** Added new criteria for use of Lorbrena after first-line Alunbrig, based on guidelines. Deleted "as the first anaplastic lymphoma kinase (ALK) inhibitor therapy" after Alecensa and Zykadia criteria, since it's not needed.	11/18/2020
Selected Revision	**Non-Small Cell Lung Cancer:** Based on FDA-approval in the first-line setting, deleted criteria requiring prior use of another ALK inhibitor therapy. Added age requirement criterion and added "as detected by an approved test" in reference to ALK mutation testing, as per the label. **Non-Small Cell Lung Cancer:** Under "Other uses with supportive evidence", moved "ROS1 Rearrangement Positive" descriptor from indication to within criteria. Added age criterion to match FDA-approved use above. Reworded criterion referring to patient has "disease progression on" to "Patient has tried at least one of". Added Rozlytrek (entrectinib capsules) as another agent patient could have tried.	03/17/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Lynparza Prior Authorization Policy
- Lynparza™ (olaparib capsules and tablets – AstraZeneca)

REVIEW DATE: 02/03/2021

OVERVIEW

Lynparza, a poly (ADP-ribose) polymerase (PARP) inhibitor, is indicated for the following:[1]

- **Breast cancer**, in adult patients with deleterious or suspected deleterious g*BRCA* mutated, HER2-negative metastatic disease, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy.
- **Ovarian cancer, treatment** in adult patients with deleterious or suspected deleterious germline BReast CAncer (g*BRCA*)-mutated advanced who have been treated with three or more prior lines of chemotherapy.
- **Ovarian cancer, maintenance** treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy.
- **Ovarian cancer, maintenance** treatment of adult patients with deleterious or suspected deleterious g*BRCA* or somatic *BRCA*-mutated advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy.
- **Ovarianc cancer, maintenance treatment in combination** with bevacizumab for adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either: a deleterious or suspected deleterious *BRCA* mutation, and/or genomic instability.
- **Pancreatic adenocarcinoma,** maintenance treatment of adult patients with deleterious or suspected deleterious g*BRCA* mutated metastatic disease, who have not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.
- **Prostate cancer**, castration-resistant (CRPC), for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic CRPC (mCRPC) who have progressed following prior treatment with Xtandi (enzalutamide tablets) or abiraterone.

Lynparza tablets and capsules are not interchangeable; they have different dosing and bioavailability. The tablet formulation yields a lower daily pill burden than the capsule formulation.

Guidelines

- **Breast Cancer:** The National Comprehensive Cancer Network (NCCN) breast cancer guidelines (version 1.2021 – January 15, 2021) recommend assessing for germline BRCA1/2 mutations in all patients with recurrent or metastatic disease to identify candidates for PARP inhibitor therapy.[3] Lynparza is noted as one of the preferred single agents for BRCA 1/2 positive tumors (category 1). It is noted that although Lynparza is FDA-approved for HER2-negative disease, the NCCN panel supports use in any breast cancer subtype with BRCA1 or BRCA2 mutation.
- **Ovarian Cancer:** The NCCN guidelines on ovarian cancer (version 2.2020 – January 12, 2021) recommend Lynparza for maintenance therapy after primary treatment in patients who have had a complete or partial response.[2] Lynparza is recommended for *BRCA* 1/2 mutations(category 1). Lynparza in combination with bevacizumab is recommended if bevacizumab was used as part of primary therapy. This combination is recommended for both *BRCA*1/2 wild-type (or unknown) [category 2A] and for germline/somatic *BRCA*1/2 mutation (category 1) in patients who have achieved a complete or partial response. The guidelines recommend use of Zejula™ (niraparib capsules), Rubraca™ (rucaparib tablets), or Lynparza as maintenance therapy options in patients with platinum-sensitive disease who have completed two or more lines of platinum-based therapy. The guidelines recommend Lynparza as one of the preferred single-agent targeted therapies for

patients with deleterious germline *BRCA* mutated advanced (persistent disease or recurrence) ovarian cancer-following three or more lines of therapy (category 2A).

- **Pancreatic Cancer:** The NCCN pancreatic adenocarcinoma guidelines (version 1.2021 – October 23, 2020) recommend Lynparza for maintenance therapy after the patient has tried first-line systemic therapy.[4] It is specifically recommended in patients who have germline *BRCA* 1/2 mutations and who have not had disease progression after at least 4 to 6 months of chemotherapy.
- **Prostate Cancer:** The NCCN prostate cancer guidelines (version 3.2020 – November 17, 2020) recommends Lynparza for HRRm in the second-line setting (category 1), after first-line treatment with Xtandi or abiraterone. In patients who have received first-line docetaxel, Lynparza is a category 2B recommended therapy in the second-line setting for HRRm. In a footnote it is noted that Lynparza is a treatment option for patients with mCRPC and a pathogenic mutation (germline and/or somatic) in a HRR gene (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L)*, who have been treated with androgen receptor-directed therapy. Patients with PPP2R2A mutation in the PROfound trial experienced an unfavorable risk-benefit profile. Therefore, Lynparza is not recommended in patients with a PPP2R2A mutations.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lynparza. All approvals are provided for 3 years in duration.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lynparza is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Breast Cancer.** Approve for 3 years if the patient meets the following criteria (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has metastatic, germline *BRCA* mutation-positive breast cancer; AND
   - **C)** Patient meets ONE of the following criteria (i or ii):
     - **i.** Patient meets BOTH of the following criteria (a and b):
       - **a)** Patient has hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND
       - **b)** Patient meets ONE of the following criteria (1 or 2):
         - **(1)** Patient has been treated with prior endocrine therapy; OR
         - **(2)** Patient is considered inappropriate for endocrine therapy; OR
     - **ii.** Patient has triple negative disease (i.e., ER-negative, PR-negative, and HER2-negative); AND
   - **D)** Patient has been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting.

2. **Ovarian Cancer – Treatment.**
   - **A)** Initial Therapy. Approve for 3 years if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has a germline *BRCA*-mutation as confirmed by an approved test; AND
     - **iii.** Patient has progressed on three or more prior lines of chemotherapy.
   - **B)** Patient is Currently Receiving Lynparza. Approve for 3 years if the patient has a *BRCA* mutation (germline) as confirmed by an approved test.

3. **Ovarian, Fallopian Tube, or Primary Peritoneal Cancer – Maintenance, Monotherapy.** Approve for 3 years if the patient meets the following criteria (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets ONE of the following (i or ii):
     - **i.** Patient meets both of the following criteria for first-line maintenance therapy (a and b):
       - **a)** Patient has a germline or somatic *BRCA* mutation-positive disease as confirmed by an approved test; AND
       - **b)** Patient is in complete or partial response to first-line platinum-based chemotherapy regimen; OR
         Note: Examples are carboplatin with paclitaxel, carboplatin with doxorubicin, docetaxel with carboplatin.
     - **ii.** Patient is in complete or partial response after at least two platinum-based chemotherapy regimens.
       Note: Examples of platinum-based chemotherapy are carboplatin with gemcitabine, carboplatin with paclitaxel, cisplatin with gemcitabine.

4. **Ovarian, Fallopian Tube, or Primary Peritoneal Cancer – Maintenance, Combination Therapy.** Approve for 3 years if the patient meets one of the following criteria (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** The medication is used in combination with bevacizumab; AND
   - **C)** Patient has homologous recombination deficiency (HRD)-positive disease as confirmed by an approved test.
     Note: HRD-positive disease includes patients with *BRCA* mutation-positive disease; AND
   - **D)** Patient is in complete or partial response to first-line platinum-based chemotherapy regimen.
     Note: Examples of chemotherapy regimens are carboplatin with paclitaxel, carboplatin with doxorubicin, docetaxel with carboplatin.

5. **Pancreatic Cancer – Maintenance Therapy.** Approve for 3 years if the patient meets the following criteria (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has a germline *BRCA* mutation-positive metastatic disease; AND
   - **C)** The disease has not progressed on at least 16 weeks of treatment with a first-line platinum-based chemotherapy regimen.

6. **Prostate Cancer – Castration-Resistant.** Approve for 3 years if the patient meets the following criteria (A, B, C, D, E, and F):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has metastatic disease; AND
   - **C)** Patient meets one of the following criteria (i or ii):
     - **i.** The medication is used concurrently with a gonadotropin-releasing hormone (GnRH) analog; OR
       Note: Examples are Lupron (leuprolide for injection), Lupron Depot (leuprolide acetate for depot suspension), Trelstar (triptorelin pamoate for injectable suspension), Zoladex (goserelin acetate implant), Vantas (histrelin acetate subcutaneous implant), Firmagon (degarelix for injection), Orgovyx (relugolix tablets).
     - **ii.** Patient has had a bilateral orchiectomy; AND
   - **D)** Patient has germline or somatic homologous recombination repair (HRR) gene-mutated disease, as confirmed by an approved test; AND
     Note: HRR gene mutations include *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*.
   - **E)** Patient does not have a *PPP2R2A* mutation; AND

F) Patient has been previously treated with abiraterone or Xtandi (enzalutamide capsules).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lynparza is not recommended in the following situations:

232. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

297. Lynparza™ capsules [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; December 2020.
298. The NCCN Ovarian Cancer Clinical Practice Guidelines in Oncology (version 2.2020 – January 12, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on. February 1, 2021.
299. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 1.2021 – January 15, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 1, 2021.
300. The NCCN Pancreatic Adenocarcinoma Clinical Practice Guidelines in Oncology (version 1.2021 – October 23, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 1, 2021.
301. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (version 3.2020 – November 17, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed February 1, 2021.
302. The NCCN Drugs & Biologics Compendium. © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 1, 2021. Search term: olaparib.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Lynparza got FDA approval for use in first-line maintenance therapy setting in *BRCA*-positive disease. Based on this indication, combined Maintenance therapy criteria for use in first-line and recurrent disease. Specified in recurrent maintenance therapy setting that Lynparza is used after at least two lines of platinum-based chemotherapy regimens.	02/06/2019
Annual Revision	New condition and criteria for Pancreatic Cancer – Maintenance Therapy was added based on FDA-approval. In Ovarian, Fallopian Tube, or Primary Peritoneal Cancer – Maintenance Therapy criteria, deleted criteria "the patient has recurrent disease."	01/15/2020
Selected Revision	Added new approval indications for Lynparza combination use with bevacizumab for maintenance therapy in ovarian cancer and for treatment of metastatic castration-resistant prostate cancer.	05/27/2020

HISTORY (CONTINUED)

Type of Revision	Summary of Changes	Review Date
Annual Revision	**All indications:** Added age criteria of ≥ 18 years. **Breast Cancer:** Deleted criteria requiring use in HER2-negative disease. The breast cancer guidelines recommend use in any subtype with *BRCA* mutation. **Prostate Cancer – Castration-Resistant:** Added Orgovyx as example in Note for GnRH analog.	02/03/2021

BRCA – BReast CAncer; HER2 – Human epidermal growth factor receptor 2; GnRH – Gonadotropin-releasing hormone.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Mekinist Prior Authorization Policy
- Mekinist™ (trametinib tablets – GlaxoSmithKline)

REVIEW DATE: 07/15/2020

OVERVIEW

Mekinist, a kinase inhibitor, is indicated for the treatment of patients with the following conditions:[1]

- **Melanoma**, in the following situations:
  - As a single agent for unresectable or metastatic disease with a BRAF V600E or V600K mutation as detected by an FDA-approved test; AND
  - In combination with Tafinlar® (dabrafenib tablets), for treatment of unresectable or metastatic disease with a BRAF V600E or V600K mutation as detected by an FDA-approved test; AND
  - In combination with Tafinlar for adjuvant treatment of patients with a BRAF V600E or V600K mutation as detected by an FDA-approved test, and involvement of lymph nodes, following complete resection.
- **Non-small cell lung cancer**, in combination with Tafinlar, for treatment of disease that has the BRAF V600E mutation as detected by an FDA-approved test.
- **Thyroid cancer**, in combination with Tafinlar, for treatment of patients with locally advanced or metastatic anaplastic disease with BRAF V600E mutation and with no satisfactory locoregional treatment options.

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines support use of Mekinst in multiple cancers.

- **Melanoma:** Guidelines (version 3.2020 – May 18, 2020) recommend BRAF/MEK inhibitor combinations for first-line (preferred if clinically needed for early response) and subsequent treatment of metastatic or unresectable melanoma with a *V600* activating mutation.[2] While combination BRAF/MEK inhibition is preferred, if a combination is contraindicated, monotherapy with a BRAF inhibitor (Tafinlar or Zelboraf® [vemurafenib tablets]) is a recommended option, particularly if the patient is not a candidate for checkpoint immunotherapy. Following resection of limited metastatic disease with a *BRAF V600*-activating mutation, BRAF/MEK combination therapy is among the treatment options for patients with no evidence of disease. Tafinlar + Mekinist® (trametinib tablets) is also recommended in guidelines as adjuvant therapy (including for nodal recurrence) in some patients with Stage III disease, including use post-surgery or use after complete lymph node dissection. If unacceptable toxicity to Tafinlar/Mekinist, other BRAF/MEK combinations can be considered. NCCN guidelines for uveal melanoma (version 1.2020 – May 21, 2020) list Mekinist as a treatment option for distant metastatic disease.[3]
- **NSCLC:** Guidelines (version 6.2020 – June 25, 2020) list Tafinlar + Mekinist among the first-line therapy and subsequent therapy options for tumors with a *BRAF* mutation.[4] NCCN also notes that

monotherapy with a BRAF inhibitor (Tafinlar or Zelboraf) is a treatment option when combination therapy is not tolerated.

- **Thyroid Cancer:** Guidelines (version 1.2020 – June 12, 2020) list Tafinlar + Mekinist as a treatment option for metastatic anaplastic thyroid cancer with a *BRAF* mutation.[5] Tafinlar and Zelboraf are also treatment options for the treatment of iodine-refractory differentiated thyroid cancer (follicular, Hürthle cell, and papillary cancer subtypes) with a *BRAF V600* mutation.
- **Ovarian, Including Fallopian Tube and Primary Peritoneal Cancer:** Guidelines (version 1.2020 – March 11, 2020) recommend Mekinist among the targeted therapy options for recurrent low-grade serous disease.[6]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Mekinist. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mekinist is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Melanoma.** Approve for 3 years if the patient meets BOTH of the following (A and B):
   - **A)** Patient has unresectable, advanced (including Stage III or Stage IV disease), or metastatic melanoma; AND
     Note: This includes adjuvant treatment in patients with Stage III disease with no evidence of disease post-surgery.
   - **B)** Patient has *BRAF V600* mutation-positive disease.

2. **Non-Small Cell Lung Cancer.** Approve for 3 years if the patient meets BOTH of the following (A and B):
   - **A)** Patient has *BRAF V600E* mutation-positive disease; AND
   - B) The agent is being used in combination with Tafinlar (dabrafenib capsules).

3. **Thyroid Cancer, Anaplastic.** Approve for 3 years if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient has locally advanced or metastatic anaplastic disease; AND
   - **B)** Mekinist will be taken in combination with Tafinlar, unless intolerant; AND
   - **C)** Patient has *BRAF V600* mutation-positive disease.

Other Uses with Supportive Evidence

4. **Ovarian/Fallopian Tube/Primary Peritoneal Cancer**. Approve for 3 years if the patient meets the following criteria (A and B):
   - **A)** Patient has recurrent disease; AND
   - **B)** The medication is used for low-grade serous carcinoma.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Mekinist is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

303. Mekinist® tablets [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; June 2020.
304. The NCCN Melanoma Clinical Practice Guidelines in Oncology (Version 3.2020 – May 18, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 2, 2020.
305. The NCCN Uveal Melanoma Clinical Practice Guidelines in Oncology (Version 1.2020 – May 21, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 2, 2020.
306. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 6.2020 – June 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 2, 2020.
307. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (Version 1.2020 – June 12, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 2, 2020.
308. The NCCN Ovarian Cancer Clinical Practice Guidelines in Oncology (Version 1.2020 – March 11, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 2, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early annual revision	Add criteria to approve for 3 years for locally advanced or metastatic anaplastic thyroid cancer that is BRAF V600-positive, if taken in combination with Mekinist (unless intolerant). Due to new indication as adjuvant therapy in resectable melanoma, remove criteria that does not allow coverage in patients who had disease progression while on a BRAF inhibitor. Remove continuation criteria in melanoma; now all approvals require that the patient has unresectable, advanced (including Stage III or Stage IV disease), or metastatic melanoma with a BRAF mutation.	05/23/2018
Annual revision	**NSCLC:** The diagnosis was changed to remove the BRAF mutation from the approval condition. The requirement that the patient has BRAF V600E mutation was added to the criteria for patients with NSCLC. **Colon or Rectal Cancer:** Add criteria as supported by NCCN colon cancer guidelines. Criteria approve if the patient has *BRAF V600E* mutation-positive disease, and if the patient has previously used chemotherapy, and if the agent will be used as part of a combination regimen for colon or rectal cancer.	06/18/2019
Annual revision	**Colon or Rectal Cancer:** This indication was removed from the policy. Mekinist is no longer a recommended therapy in guidelines for colon and rectal cancer. **Ovarian/Fallopian Tube/Primary Peritoneal Cancer:** Based on guidelines, this indication was added as an off-label use. Criteria approve for 3 years, if the patient has recurrent low-grade serous carcinoma.	07/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Mektovi Prior Authorization Policy

- Mektovi® (binimetinib tablets – Array BioPharma)

REVIEW DATE: 07/15/2020

OVERVIEW

Mektovi, a kinase inhibitor, is indicated in combination with Braftovi® (encorafenib capsules) for treatment of unresectable or metastatic melanoma with a *BRAF V600E* or *V600K* mutation as detected by an FDA-approved test.[1]

Guidelines

Guidelines (version 3.2020 – May 18, 2020) recommend BRAF/MEK inhibitor combinations for first-line (preferred if clinically needed for early response) and subsequent treatment of metastatic or unresectable melanoma with a *V600* activating mutation.[2] While combination BRAF/MEK inhibition is preferred, if a combination is contraindicated, monotherapy with a BRAF inhibitor (Tafinlar® [dabrafenib capsules] or Zelboraf® [vemurafenib tablets]) is a recommended option, particularly if the patient is not a candidate for checkpoint immunotherapy. Following resection of limited metastatic disease with a *BRAF V600*-activating mutation, BRAF/MEK combination therapy is among the treatment options for patients with no evidence of disease. Tafinlar + Mekinist® (trametinib tablets) is also recommended in guidelines as adjuvant therapy (including for nodal recurrence) in some patients with Stage III disease, including use post-surgery or use after complete lymph node dissection. If unacceptable toxicity to Tafinlar/Mekinist, other BRAF/MEK combinations can be considered.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Mektovi. All approvals are provided the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mektovi is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Melanoma.** Approve for 3 years if the patient meets ALL of the following (A, B, and C):
   - **C)** Patient has unresectable, advanced, or metastatic melanoma; AND
   - **D)** Patient has *BRAF V600* mutation-positive disease; AND
   - **E)** Mektovi will be used in combination with Braftovi (encorafenib capsules).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Mektovi is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

309. Mektovi® tablets [prescribing information]. Boulder, CO: Array BioPharma; January 2019.
310. The NCCN Melanoma Clinical Practice Guidelines in Oncology (Version 3.2020 – May 18, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	06/27/2018
Annual revision	**Colon or Rectal Cancer:** Add criteria as supported by NCCN colon cancer guidelines. Criteria approve if the patient has *BRAF V600E* mutation-positive disease, and if the patient has previously used chemotherapy, and if the agent will be used as part of a combination regimen for colon or rectal cancer.	06/18/2019
Annual revision	**Colon or Rectal Cancer:** This indication was removed from the policy. Mektovi is no longer a recommended therapy in guidelines for colon and rectal cancer.	07/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Nerlynx Prior Authorization Policy

- Nerlynx™ (neratinib tablets – Puma Biotechnology)

REVIEW DATE: 09/23/2020

OVERVIEW

Nerlynx is indicated for the extended adjuvant treatment of adult patients with early-stage human epidermal growth factor receptor 2 (HER2) overexpressed/amplified (i.e., HER2 positive [HER2+]) breast cancer, to follow adjuvant trastuzumab -based therapy.[1] It is also indicated in combination with capecitabine for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting. Nerlynx is a kinase inhibitor that irreversibly binds to epidermal growth factor receptors (EGFR), HER2, and HER4. *In vitro* studies showed Nerlynx has antitumor activity in EGFR and/or HER2 expressing carcinoma cell lines.

Clinical Efficacy

The efficacy of Nerlynx was established in one Phase III pivotal study (ExteNET, Extended Adjuvant Treatment of Breast Cancer with Neratinib) in women with early stage HER2+ breast cancer (n = 2,840).[1,2] In a prespecified exploratory subgroup analysis of invasive disease-free survival (iDFS), Nerlynx was more beneficial in patients with hormone receptor(HR)-positive breast cancer (unstratified hazard ratio 0.49; 95% 0.31, 0.75) than in patients with HR-negative disease (unstratified hazard ratio 0.93; 95% confidence interval [CI]: 0.60, 1.43). In another analysis after a median follow-up of 5.2 years iDFS survival was 90·2% in the Nerlynx group and 87·7% in the placebo group.

An exploratory analysis was conducted to understand why the subgroup of patients with HR-negative disease did not show statistical significance for efficacy in the ExteNET trial.[5] It is hypothesized that the risk of disease recurrence is highest during the first 6 months following completion of trastuzumab therapy

in patients with HR-negative, HER2+ disease; so the greatest benefit with Nerlynx would likely also be in this subgroup of patients completing trastuzumab within 6 months of initiating Nerlynx in the study. The 5-year iDFS for patients with interval 0 to 6 months between prior trastuzumab therapy and Nerlynx randomization in the study was 88.9% for Nerlynx and 86.1% for placebo (HR 0.73; 95% CI: 0.47, 1.14). For interval duration > 6 months, the iDFS for Nerlynx at 5 years was 88.7% compared with 92.7% for placebo (HR 1.52; 95% CI: 0.82, 2.88).

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on breast cancer (version 6.2020 – September 8, 2020) notes that Nerlynx can be considered as extended adjuvant therapy following adjuvant trastuzumab-containing therapy in patients with HR+, HER2+ disease with a perceived high risk of recurrence (such as Stage II or III breast cancer) [category 2A].[4] The benefits or toxicities associated with extended Nerlynx in patients who have received Perjeta is unknown. The guidelines do not include recommendations for using Nerlynx extended adjuvant therapy in patients with HR-negative, HER2+ disease. For the treatment of recurrent or metastatic disease, Nerlynx + capecitabine is listed as a category 2A recommended option under "other recommended regimens".

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Nerlynx. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nerlynx is recommended in those who meet the following criteria:

FDA-Approved Indications

~~6.~~3. **Breast Cancer – Adjuvant Therapy.** Approve for 1 year (total) if the patient meets the following criteria (A and B):
- **A)** Patient has human epidermal growth factor receptor 2 (HER2)-positive breast cancer; AND
- **B)** Patient meets ONE of the following criteria (i or ii):
  - **i.** The medication is requested for extended adjuvant therapy after the patient has completed 1 year of adjuvant therapy with trastuzumab intravenous products; OR
  - **ii.** Patient has tried adjuvant therapy with trastuzumab intravenous products and could not tolerate 1 year of therapy, according to the prescriber.

2. **Breast Cancer – Advanced or Metastatic Disease.** Approve for 3 years if the patient meets the following criteria (A, B, and C):
- **A)** Patient has human epidermal growth factor receptor 2 (HER-2)-positive breast cancer; AND
- **B)** The medication is used in combination with capecitabine; AND
- **C)** Patient has tried at least two prior anti-HER2 based regimens in the metastatic setting.
  Note: Examples include Perjeta (pertuzumab injection for intravenous use) + trastuzumab + docetaxel, Perjeta + trastuzumab + paclitaxel; Kadcyla (ado-trastuzumab emtansine for intravenous use), trastuzumab + capecitabine, Tykerb (lapatinib tablets) + capecitabine, trastuzumab + Tykerb.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nerlynx is not recommended in the following situations:

233. Concurrent Use of Nerlynx with Other Medications for Adjuvant or Neoadjuvant Treatment of HER2-Positive Breast Cancer: Nerlynx is not indicated in combination with other medications for adjuvant or neoadjuvant (preoperative) HER2 positive breast cancer (e.g., Herceptin, Perjeta). Studies are not available for this use. Patients with HR+ early breast can receive concurrent adjuvant endocrine therapy.[2]

234. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

311. Nerlynx™ tablets [prescribing information]. Los Angeles, CA: Puma Biotechnology, Inc.; July 2020.
312. Chan A, Delaloge S, Holmes FA, et al; ExteNET Study Group. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2016;17:367-377.
313. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 6.2020 – September 8, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 21, 2020.
314. Martin M, Holmes FA, Ejlertsen B, et al; for the ExteNet Study Group. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18(12):1688-1700.
5. Ejlertsen B, Barrios CH, Gokmen E, et al. Timing of initiation of neratinib after trastuzumab-based adjuvant therapy in early-stage HER2+ hormone receptor (HR)-negative breast cancer: exploratory analysis from the phase III ExteNET trial [Abstract 549]. Presented at 2018 ASCO Annual Meeting. June 2, 2018.

HISTORY

Type of Revision	Summary of Changes*	Review Date
New Policy	New policy	08/23/2017
Selected Revision	Breast cancer in women and in men: added the patient has hormone receptor-positive (that is, estrogen- and/or progesterone-positive) breast cancer. In Conditions Not Recommended for Approval, added Use of Nerlynx For a Total of No Greater than 1 Year Duration During a Patient's Lifetime.	01/03/2018
Update	02/12/2018: Conditions Not Recommended for Approval: In Concurrent Use of Nerlynx with Other Medications for Adjuvant or Neoadjuvant Treatment of HER2-Positive Breast Cancer, the last sentence was revised to replace the word"estrogen" with "endocrine".	NA
Annual Revision	No criteria changes	09/19/2018
Annual Revision	Deleted "Breast Cancer in Men" condition since the criteria are the same for all adult patients. Deleted "in Women" for the approval condition "Breast Cancer". Changed approval duration to "1 year (total)" from "up to 1 year". Deleted criteria "The patient has early stage disease", since it is not needed. Deleted "Herceptin" and referred to it by chemical name due to the availability of biosimilars. Added criteria that "The medication is requested for extended adjuvant therapy" after the patient has 1 year of trastuzumab therapy. Changed from "prescribing physician" to "prescriber".	09/25/2019
Selected Revision	The requirement specifying Nerlynx use only in hormone receptor-positive disease was removed.	12/18/2019
Selected Revision	Added new FDA approved indication for Nerlynx use in advanced or metastatic breast cancer. Deleted condition for 1-year maximum lifetime approval listed under "Conditions Not Recommended for Approval", since this is covered in the criteria for approval already.	03/04/2020
Annual Revision	No criteria changes.	09/23/2020

NA - Not applicable.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology - Nexavar® (sorafenib tablets – Bayer/Onyx)

DATE REVIEWED: 05/20/2020

OVERVIEW

Nexavar, a kinase inhibitor, is indicated for the treatment of patients with unresectable hepatocellular carcinoma (HCC), treatment of patients with advanced renal cell carcinoma (RCC), and for the treatment of patients with locally recurrent or metastatic, progressive, differentiated thyroid carcinoma (DTC) that is refractory to radioactive iodine treatment.[1] Nexavar decreases tumor cell proliferation *in vitro*, and was shown to inhibit multiple intracellular and cell surface kinases, several of which are thought to be involved in tumor cell signaling, angiogenesis, and apoptosis.

Guidelines

The National Comprehensive Cancer Network (NCCN) Compendium recommends Nexavar use for acute myeloid leukemia, for hepatobiliary cancer, kidney cancer, thyroid cancer, ovarian cancer, bone cancer, and soft tissue sarcoma.[2]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Nexavar. All approvals are provided for 3 years.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nexavar is recommended in those who meet the following criteria:

FDA-Approved Indications

~~7.~~4. **Renal Cell Carcinoma (RCC).** Approve for 3 years in patients who meet the following criteria (A and B):
- **A)** The patient has relapsed or Stage IV clear cell histology RCC; AND
- **B)** The patient has tried at least one prior systemic therapy.
  Note: Examples include Inlyta (axitinib tablets), Votrient (pazopanib tablets), Sutent (sunitinib capsules), Cabometyx (cabozantinib tablets).

~~8.~~5. **Differentiated (i.e. papillary, follicular, and Hürthle cell) Thyroid Carcinoma.** Approve for 3 years if refractory to radioactive iodine therapy.

~~9.~~6. **Hepatocellular Carcinoma (HCC), Unresectable.** Approve for 3 years.

Other Uses with Supportive Evidence

~~10.~~7. **Acute Myeloid Leukemia (AML).** Approve for 3 years if disease is *FLT3*-ITD mutation-positive as detected by an approved test.

~~11.~~8. **Angiosarcoma.** Approve for 3 years.

~~12.~~9. **Chordoma.** Approve for 3 years in patients with recurrent disease.

~~13.~~10. **Desmoid Tumors (aggressive fibromatosis).** Approve for 3 years.

~~14.~~11. **Gastrointestinal Stromal Tumor (GIST).** Approve for 3 years if the patient meets the following criteria (A, B, and C):

C) Patient has previously tried imatinib (Gleevec® tablets, generics); AND
D) Patient has previously tried Sutent (sunitinib capsules); AND
E) Patient has previously tried Stivarga® (regorafenib tablets).

~~15.~~12. **Medullary Thyroid Carcinoma.** Approve for 3 years if the patient has tried Caprelsa® (vandetanib tablets) or Cometriq® (cabozantinib capsules).

~~16.~~13. **Ovarian, Fallopian Tube, Primary Peritoneal Cancer**. Approve for 3 years if the patient meets the following criteria (A and B):

A) The patient has platinum-resistant disease; AND
B) Nexavar is used in combination with topotecan.

~~17.~~14. **Osteosarcoma**. Approve for 3 years if the patient meets the following criteria (A and B):

C) Patient has tried chemotherapy; AND
D) Patient has relapsed/refractory or metastatic disease.

~~18.~~15. **Solitary Fibrous Tumor and Hemangiopericytoma.** Approve for 3 years.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Nexavar has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

235. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

339. Nexavar® tablets [prescribing information]. Wayne, NJ: Bayer; December 2017.
340. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 18, 2020. Search term: sorafenib.

HISTORY

Type of Revision	Summary of Changes*	Date Reviewed
Annual revision	Renal Cell Carcinoma: Criterion was revised to add that it includes predominant clear cell and non-clear cell histology. Differentiated Thyroid Cancer: Criteria were revised to only require that the patient's disease is refractory to radioactive iodine therapy. Acute Myeloid Leukemia: Criteria were revised to remove all the required conditions of approval. Medullary Thyroid Cancer: Criteria were revised to remove the requirement that the patient has progressive disease or symptomatic distant metastases. Osteosarcoma: Criterion regarding the requirement to try standard chemotherapy was revised to remove the word "standard". Conditions Not Recommended for Approval: Liposarcoma was deleted and the indication, Pancreatic Cancer was changed to Pancreatic Adenocarcinoma.	02/10/2016
Annual revision	Criteria for Chordoma added to Other Uses.	03/08/2017
Annual revision	Solitary Fibrous Tumor and Hemangiopericytoma: New indication was added. Conditions Not Recommended for Approval: Removed Leiomyosarcoma, Lymphoma, and Melanoma.	04/11/2018
Annual revision	• Deleted all conditions listed under "Conditions Not Recommended for Approval." • Ovarian, Fallopian Tube, Primary Peritoneal Cancer. Added new approval condition based on compendium/guidelines. • Desmoid Tumors. Deleted "in patients with advanced or unresectable tumors" since it can be used for resectable tumors. • Acute Myeloid Leukemia. Added if"disease is FLT3-ITD mutation-positive based on approved test" according to compendium/guidelines. • Renal Cell Carcinoma (RCC): Deleted "Advanced, (Predominant Clear Cell or Non-Clear Cell Histology)" as condition qualifiers. Added criteria patient has "relapsed or Stage IV clear cell RCC" and patient has tried one prior systemic therapy. No longer used in non-clear cell.	05/08/2019
Annual revision	• No criteria changes	5/20/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Nilutamide Prior Authorization Policy

- Nilandron (nilutamide tablets – Concordia Pharmaceuticals Inc., generic)

REVIEW DATE: 01/13/2021

OVERVIEW

Nilutamide, in combination with surgical castration, is indicated for the treatment of **metastatic prostate cancer (Stage D_2)**.[1] For maximum benefit, nilutamide treatment must begin on the same day as or on the day after surgical castration.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (version 3.2020 – November 17, 2020) recommend nilutamide in combination with luteinizing hormone-releasing hormone (LHRH) agonists [Lupron® (leuprolide for injection), Lupron Depot® (leuprolide acetate for depot suspension), Trelstar® (triptorelin pamoate for injectable suspension), Zoladex® (goserelin acetate implant), Vantas® (histrelin acetate subcutaneous implant)] with or without external beam radiation therapy for androgen deprivation therapy.[2,3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of nilutamide tablets. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of nilutamide is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Prostate Cancer.** Approve for 3 years if nilutamide is used concurrently with a luteinizing hormone-releasing hormone (LHRH) agonist.
   Note: Examples are Lupron (leuprolide for injection), Lupron Depot (leuprolide acetate for depot suspension), Trelstar (triptorelin pamoate for injectable suspension), Zoladex (goserelin acetate implant), Vantas (histrelin acetate subcutaneous implant).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of nilutamide is not recommended in the following situations:

236. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

246. Nilandron® [prescribing information]. St. Micheal, Barbados: Concordia Pharmaceutical Inc.; May 2017.
247. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (Version 3.2020 – November 17, 2020). © 2020 National Comprehensive Cancer Network Inc. Available at: http://www.nccn.org. Accessed December 30, 2020.
248. The NCCN Drugs & Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 30, 2020. Search term: nilutamide.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/18/2019
Annual Revision	No criteria changes.	01/13/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Ninlaro Prior Authorization Policy

- Ninlaro® (ixazomib capsules – Takeda)

REVIEW DATE: 03/10/2021

OVERVIEW

Ninlaro, an oral proteasome inhibitor, is indicated in combination with Revlimid® (lenalidomide capsules) and dexamethasone for treatment of patients with **multiple myeloma** who have received at least one prior therapy.[1] Ninlaro should be taken once a week on the same day and at approximately the same time for the first 3 weeks of a 4-week cycle. There are dose modification guidelines which are recommended to manage treatment-related adverse events, including platelet count, absolute neutrophil count (ANC), and other toxicities (e.g., rash, peripheral neuropathy). Treatment should be continued until disease progression or unacceptable toxicity. Safety and efficacy are not established in patients < 18 years of age.

Guidelines

Ninlaro is discussed in various guidelines from the National Comprehensive Cancer Network (NCCN).

- **Multiple Myeloma:** NCCN guidelines (version 4.2021 – December 10, 2020) list multiple therapeutic regimens that may be used for primary therapy and previously treated multiple myeloma.[2] Ninlaro/Revlimid/dexamethasone is an other recommended regimen (transplant and non-transplant candidates), and Ninlaro/cyclophosphamide/dexamethasone is useful in certain circulstances (transplant candidates). Maintenance with Ninlaro is also listed among the alternatives for transplant candidates. For previously treated disease, multiple regimens are listed, including Ninlaro/Revlimid/dexamethasone (preferred), Ninlaro/Pomalyst/dexamethasone (preferred), Ninlaro/cyclophosphamide/dexamethasone, Ninlaro/dexamethasone.
- **Systemic Light Chain Amyloidosis:** NCCN guidelines (version 2.2021 – February 8, 2021) list Ninlaro ± dexamethasone among the treatment options for patients who have relapsed/refractory disease.[3]
- **Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma:** NCCN guidelines (version 1.2021 – September 1, 2020) list Ninlaro/rituximab/dexamethasone among the treatment options for primary therapy.[4]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Ninlaro. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ninlaro is recommended in those who meet the following criteria:

FDA-Approved Indications

~~19.~~16. **Multiple Myeloma.** Approve for 3 years if the patient meets BOTH of the following (A and B):
- **13.** Patient is ≥ 18 years of age; AND
- **14.** Patient meets one of the following (i, ii, or iii):
  - **i.** Ninlaro will be taken in combination with Revlimid (lenalidomide capsules) and dexamethasone; OR
  - **ii.** Patient has received at least ONE prior regimen for multiple myeloma; OR
    Note: Examples include regimens containing Velcade (bortezomib injection), Kyprolis (carfilzomib infusion), Revlimid (lenalidomide capsules), Darzalex (daratumumab injection).
  - **iii.** The medication will be used following autologous stem cell transplantation (ASCT).

Other Uses with Supportive Evidence

~~20.~~17. **Systemic Light Chain Amyloidosis.** Approve for 3 years if the patient meets BOTH of the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has tried at least one other regimen for this condition.
  Note: Examples of agents used in other regimens include Velcade (bortezumab injection), Revlimid (lenalidomide capsules), cyclophosphamide, and melphalan.

~~21.~~18. **Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma.** Approve for 3 years if the patient meets BOTH of the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The medication is used in combination with a rituximab product and dexamethasone.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ninlaro is not recommended in the following situations:

237. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

341. Ninlaro® capsules [prescribing information]. Cambridge, MA: Takeda Pharmaceutical Company Limited; February 2020.
342. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (version 4.2021 – December 10, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 5, 2021.
343. The NCCN Systemic Light Chain Amyloidosis Clinical Practice Guidelines in Oncology (version 2.2021 – February 8, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 5, 2021.
344. The NCCN Waldenstrom Macroglobulinemia/Lymphoblastic Lymphoma Clinical Practice Guidelines in Oncology (version 1.2021 – September 1, 2020). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 5, 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Multiple Myeloma:** Add a criterion to approve if being used following autologous stem cell transplantation. Examples of agents for multiple myeloma were updated in the criteria. **Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma:** Add this condition as an off-label approval, if taken in combination with a rituximab product and dexamethasone.	02/26/2020
Annual Revision	**Multiple Myeloma:** To be consistent with other oral oncology policies, the requirement that the patient is ≥ 18 years of age was added to the criteria. **Systemic Light Chain Amyloidosis:** To be consistent with other oral oncology policies, the requirement that the patient is ≥ 18 years of age was added to the criteria. **Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma:** To be consistent with other oral oncology policies, the requirement that the patient is ≥ 18 years of age was added to the criteria.	03/10/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Nubeqa Prior Authorization Policy
- Nubeqa (darolutamide tablets – Bayer HealthCare Pharmaceuticals Inc.)

REVIEW DATE: 08/26/2020

OVERVIEW
Nubeqa, an androgen receptor inhibitor, is indicated for the treatment of patients with non-metastatic, castration-resistant prostate cancer (nmCRPC).[1]

GUIDELINES
According to the National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer, (version 2.2020 – May 21, 2020) for nmCRPC, androgen deprivation therapy (ADT) is continued to maintain castrate serum levels of testosterone (< 50 ng/dL).[2] Nubeqa, Erleada™ (apalutamide tablets) and Xtandi® (enzalutamide capsules) are all category 1 preferred regimens especially if the prostate specific antigen doubling time (PSADT) is ≤ 10 months. Observation is noted as an option especially if the PSADT is > 10 months.

POLICY STATEMENT
Prior authorization is recommended for prescription benefit coverage of Nubeqa. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Nubeqa is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Prostate Cancer – Non-Metastatic, Castration-Resistant.** Approve for 3 years if the patient meets the following criteria (A or B):
   A) The medication is used concurrently with a gonadotropin-releasing hormone (GnRH) analog; OR

Note: Examples are Lupron (leuprolide for injection), Lupron Depot (leuprolide acetate for depot suspension), Trelstar (triptorelin pamoate for injectable suspension), Zoladex (goserelin acetate implant), Firmagon (degarelix for injection), Vantas (histrelin acetate subcutaneous implant).

B) Patient has had a bilateral orchiectomy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nubeqa is not recommended in the following situations:

238. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

249. Nubeqa® [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceutical Inc.; July 2019.
250. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (Version 2.2020 – May 21, 2020). © 2020 National Comprehensive Cancer Network Inc. Available at: http://www.nccn.org. Accessed August 17, 2020.

HISTORY

Type of Revision	Summary of Changes*	Review Date
New Policy	New criteria	07/31/2019
Selected Revision	Added criteria requiring concomitant use of GnRH agonist with Nubeqa or the patient must have had bilateral orchiectomy, as per Nubeqa prescribing information.	10/09/2019
Annual Revision	**Prostate Cancer – Non-Metastatic Castration-Resistant:** Changed gonadotropin releasing-hormone "agonist" to "analog". Firmagon was added to the list of examples in the Note.	08/26/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Odomzo Prior Authorization Policy

- Odomzo® (sonidegib capsules – Novartis)

REVIEW DATE: 11/04/2020

OVERVIEW

Odomzo, a hedgehog pathway inhibitor, is indicated for the treatment of adults with locally advanced **basal cell carcinoma** that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy.[1] It is an inhibitor of the hedgehog signaling pathway, where it binds to and inhibits Smoothened, a transmembrane protein involved in Hedgehog signal transduction.

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines for basal cell carcinoma (version 1.2020 – October 24, 2019) note that surgical approaches offer the most effective and efficient means for accomplishing a cure; radiation therapy may be chosen as the primary treatment in order to achieve optimal overall results.[2] For residual disease when surgery and radiation therapy are contraindicated and for recurrent disease with distant metastases, a hedgehog pathway inhibitor should be considered.

Other Uses with Supportive Evidence

Although Odomzo is not indicated in metastatic basal cell carcinoma, the pivotal study enrolled adults with histologically confirmed metastatic basal cell carcinoma for which all existing treatment options had been exhausted.[1] In this study, an objective response was obtained by 15% of patients (n = 2/13) patients who were treated with Odomzo 200 mg.[3] In the 12-month analysis, response rates by central review were 7.7% and 17.4% in the Odomzo 200 mg and 800 mg groups, respectively. Disease control rate was 92% in patients treated with either dose of Odomzo. Guidelines for basal cell carcinoma list hedgehog pathway inhibitors (i.e., Erivedge, Odomzo) as treatment options for patients with metastatic basal cell carcinoma.[2]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Odomzo. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Odomzo is recommended in those who meet the following criteria:

FDA-Approved Indications

~~22.~~19. **Basal Cell Carcinoma, Locally Advanced.** Approve for 3 years if the patients meets ONE of the following conditions (A or B):

~~15.~~ Initial Therapy. Approve if the patient meets ONE of the following (i or ii):

- **i.** Patient has recurrent basal cell carcinoma following surgery or radiation therapy; OR
- **ii.** Patient meets BOTH of the following (a and b):
  - ~~a)~~ Patient is not a candidate for surgery; AND
  - ~~b)~~ According to the prescriber, the patient is not a candidate for radiation therapy.

16. Patient is Currently Receiving Odomzo. Approve.

Other Uses with Supportive Evidence

~~23.~~20. **Basal Cell Carcinoma, Metastatic.** Approve for 3 years.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Odomzo is not recommended in the following situations:

239. Basal Cell Carcinoma (Locally Advanced or Metastatic), in Patients with Disease Progression While on Erivedge (vismodegib capsules). [Note: This does not apply to patients already started on Odomzo. Refer to criteria for BCC, Locally Advanced for Patients Currently Receiving Odomzo.] Results from an open-label study (n = 9) showed resistence to Odomzo in patients with advanced BCC who had progressed while taking Erivedge.[6] There are no data to support the use of Odomzo in patients who have experienced disease progression on Erivedge. Previous use of a hedgehog inhibitor was not allowed in the pivotal study for Odomzo.[3] Patients who develop resistance to one of the hedgehog pathway inhibitors are not expected to respond to another hedgehog pathway inhibitor.

240. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

345. Odomzo® capsules [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; May 2019.
346. The NCCN Basal Cell Skin Cancers Clinical Practice Guidelines in Oncology (version 1.2020 – October 24, 2019). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 28, 2020.
347. Migden MR, Guminski A, Gutzmer R, et al. Treatment with two different doses of sonidegib in patients with locally advanced or metastatic basal cell carcinoma (BOLT): a multicentre, randomised, double-blind phase 2 trial. *Lancet Oncol*. 2015;16(6):716-728.
348. Erivedge® capsules [prescribing information]. South San Fransisco, CA: Genentech/Roche; July 2020.

349. Danial C, Sarin KY, Oro AE, Chang AL. An investigator-initiated open-label trial of sonidegib in advanced basal cell carcinoma patients resistant to vismodegib. *Clin Cancer Res*. 2016;22(6):1325-1329.
350. Dummer R, Guminski A, Gutzmer R, et al. The 12-month analysis from Basal Cell Carcinoma Outcomes with LDE225 Treatment (BOLT): A phase II, randomized, double-blind study of sonidegib in patients with advanced basal cell carcinoma. *J Am Acad Dermatol*. 2016;75(1):113-125.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Patients Already Started on Odomzo:** This criterion only applies to BCC, locally advanced disease; reformat to address in the criteria section for this condition. **Conditions Not Recommended for Coverage:** Remove Solid Tumors Other than Basal Cell Carcinoma from this section of the policy. This indication remains a denial but is not specifically listed in the policy.	10/10/2018
Annual Revision	No criteria changes.	10/16/2019
Annual Revision	**Basal Cell Carcinoma, Locally Advanced:** For the criterion applying to a patient who is not a candidate for radiation therapy, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician).	11/04/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Onureg Prior Authorization Policy
- Onureg® (azacitadine tablets – Celgene Corporation)

REVIEW DATE: 09/16/2020; selected revisions 11/18/2020

OVERVIEW
Onureg, a nucleoside metabolic inhibitor, is indicated for the continued treatment of **acute myeloid leukemia** (AML) in adults who achieve first complete remission or complete remission with incomplete blood count recovery following intensive induction chemotherapy and are unable to complete intensive curative therapy.[1]

Guidelines
The National Comprehensive Cancer Network (NCCN) AML guidelines (version 1.2021 – October 22, 2021) recommend Onureg for the post-remission maintenance treatment of AML in patients < 60 years of age with intermediate- or poor-risk cytogenetics who decline or not fit or eligible for allogeneic hematopoietic stem cell transplantation or in patients ≥ 60 years of age following complete response to intensive therapy.[2,3]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Onureg. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Onureg is recommended in those who meet the following criteria:

FDA-Approved Indications

140. Acute Myeloid Leukemia. Approve for 3 years if the patient meets the following criteria (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) The medication is used for post-remission maintenance therapy; AND

C) According to the prescriber, the patient meets one of the following (i or ii):

i. Patient has intermediate- or poor-risk cytogenetics who decline or are not fit or eligible for allogeneic hematopoietic stem cell transplant; OR
Note: Examples of intermediate- and poor-risk cytogenetics include the following genetic alterations: wild-type *NPM1* without *FLT3-ITD* or with *FLT3-ITD^{low}*, *MLLT3-KMT2A*, *DEK-NUP214*, and *KMT2A* rearranged.

ii. Patient has complete response to previous intensive induction chemotherapy; AND
Note: Examples of intensive chemotherapy include Venclexta plus subcutaneous azacitidine or Venclexta plus intravenous decitabine.

D) Patient is not able to complete intensive consolidation chemotherapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Onureg is not recommended in the following situations:

152. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

476. Onureg tablets [prescribing information]. Summit, NJ: Celgene Corporation; September 2020.
477. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (version 1.2021 – October 14, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed October 22, 2020.
478. The NCCN Drugs & Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed October 21, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	09/16/2020
Selected revision	**Acute Myeloid Leukemia.** Removed criteria for use following intensive induction chemotherapy in patient who achieve first complete response or first complete response with incomplete blood count recovery. Added criteria for use as post-remission maintenance therapy; and for use in patients with intermediate- or poor-risk cytogenetics who decline or are not fit or eligible for allogeneic hematopoietic stem cell transplant or in patients with complete response to previous intensive chemotherapy.	11/18/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Orgovyx Prior Authorization Policy

- Orgovyx™ (relugolix tablets – Myovant Sciences)

REVIEW DATE: 12/29/2020; 01/20/2021 selected revision

OVERVIEW

Orgovyx, a gonadotropin-releasing hormone (GnRH) receptor antagonist, is indicated for the treatment of adult patients with **advanced prostate cancer**.[1]

Guidelines

Orgovyx is not addressed in the guidelines. The National Comprehensive Cancer Network (NCCN) prostate cancer guidelines (version 3.2020 – November 17, 2020) recommend the use of leutinizing hormone-releasing hormone (LHRH) agonist or antagonist in various stages of the disease. These agents are used for androgen deprivation therapy, to lower and maintain castration levels of testosterone (< 50 ng/dL) in men with prostate cancer.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Orgovyx. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Orgovyx is recommended in those who meet the following criteria:

FDA-Approved Indications

4. Prostate Cancer. Approve for 3 years if the patient meets the following criteria (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has advanced disease.
  Note: Advanced disease is defined as disease that has spread to other parts of the body, beyond the prostate. It can also include patients with persistent prostate specific antigen (PSA) levels or rising PSA levels after radiotherapy or surgery. Metastatic disease is also considered as advanced disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Orgovyx is not recommended in the following situations:

153. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

479. Orgovyx tablets [prescribing information]. Brisbane, CA: Myovant Sciences, Inc.; December, 2020.
480. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (version 3.2020 – November 17, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 18, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/29/2020
Selected Revision	**Prostate Cancer:** Added the following to the existing Note to further define advanced disease: "It can also include patients with persistent prostate specific antigen (PSA) levels or rising PSA levels after radiotherapy or surgery".	01/20/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Pemazyre™ (pemigatinib tablets – Incyte Corporation)

DATE REVIEWED: 04/22/2020

OVERVIEW

Pemazyre is indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test.[1] This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Guidelines

Pemazyre is not addressed in the guidelines. According to the National Comprehensive Cancer Network (NCCN) hepatobiliary guidelines (version 1.2020 – March 23, 2020), for primary treatment of unresectable and metastatic disease, gemcitabine + cisplatin is the category 1 preferred regimen. Upon disease progression, FOLFOX is the preferred subsequent therapy regimen (category 2A). Other recommended regimens are FOLFIRI (category 2B) or Stivarga (regorafenib tablets) [category 2B]. For neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion-positive tumors, Vitrakvi (larotrectinib capsules) and Rozlytrek (entrectinib capsules) are recommended (both category 2A); Keytruda (pembrolizumab for injection) is recommended for microsatellite instability high (MSI-H) and mismatch repair-deficient (dMMR) tumors (category 2A).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Pemazyre. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Pemazyre is recommended in those who meet the following criteria:

FDA-Approved Indications

17. Cholangiocarcinoma. Approve for 3 years if the patient meets the following criteria (A and B):
- **A)** The patient has unresectable locally advanced or metastatic disease with a fibroblast growth factor receptor 2 (*FGFR2*) fusion or other rearrangement, as detected by an approved test; AND
- **B)** The patient has been previously treated with at least one systemic therapy regimen.
  Note: Examples are gemcitabine + cisplatin, 5-fluorouracil + oxaliplatin or cisplatin, capecitabine + oxaliplatin or cisplatin, gemcitabine + Abraxane or capecitabine or oxaliplatin, FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Pemazyre has not been shown to be effective or there are limited or preliminary data that are not supportive of general approval for the following conditions.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

5. Pemazyre™ tablets [prescribing information]. Wilmington, DE: Incyte Corporation; April 2020.

6. The NCCN Hepatobiliary Cancers Clinical Practice Guidelines in Oncology (Version 1.2020 – March 23, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on April 19, 2020.

HISTORY

Type of Revision	Summary of Changes*	Date Reviewed
New policy	New criteria	04/22/2020
Update	5/6/2020: Added "fusion" after (FGFR2) for clarity, as per the label.	--

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Piqray® (alpelisib tablets – Novartis Pharmaceuticals Corporation)

DATE REVIEWED: 06/10/2020

OVERVIEW

Piqray is indicated in combination with fulvestrant injection for the treatment of postmenopausal women and men with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, phosphatidylinositol-3-kinase (*PIK3CA*)-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.[1] Patients treated with Piqray should have one or more *PIK3CA* mutations in tumor tissue or plasma specimens. If no mutation is detected in a plasma specimen, tumor tissue should be tested. Information on FDA-approved tests for the detection of *PIK3CA* mutations in breast cancer is available on the FDA website.[2]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on breast cancer (version 4.2020 – May 8, 2020) recommend Piqray, in combination with fulvestrant, as a preferred regimen (category 1) for *PIK3CA*-mutated tumors in postmenopausal or premenopausal patients (receiving ovarian ablation or suppression, if premenopausal) with HR+/HER2-negative, recurrent or Stage IV disease.[3] It is noted that the safety of Piqray in patients with Type 1 or uncontrolled Type 2 diabetes has not been established. Other preferred regimens for HR+/HER2-negative disease include the following: fulvestrant, aromatase inhibitor (i.e., letrozole, anastrozole, exemestane) + CDK4/6 inhibitor (i.e., Ibrance® [palbociclib capsules], Kisqali® [ribociclib tablets], Verzenio™ [abemaciclib tablets]), fulvestrant + CDK4/6 inhibitor (all category 1), aromatase inhibitor monotherapy, tamoxifen or toremifene, exemestane + Afinitor® (everolimus tablets), fulvestrant + Afinitor, and tamoxifen + Afinitor (all category 2A). Of note, men with breast cancer are treated similarly to postmenopausal women.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Piqray. All approvals are provided for the duration noted below. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: a woman is defined as an individual with the biological traits of a woman, regardless of the individual's gender identity or gender expression; men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Piqray is recommended in those who meet the following criteria:

FDA-Approved Indications

18. Breast Cancer. Approve for 3 years if the patient meets the following criteria (A, B, C, D, E, and F):
- **A)** The patient meets one of the following criteria (i or ii):
  - **i.** The patient is a postmenopausal female* or a male*; OR
  - **ii.** The patient is premenopausal* and is receiving ovarian suppression with a gonadotropin-releasing hormone (GnRH) analog or has had surgical bilateral oophorectomy or ovarian irradiation.
    Note: Examples include Lupron/Lupron Depot (leuprolide acetate injectable suspension), Trelstar (triptorelin pamoate injectable suspension), Zoladex (goserelin acetate implant); AND
- **B)** The patient has advanced or metastatic hormone receptor (HR)-positive disease; AND
- **C)** The patient has human epidermal growth factor receptor 2 (HER2)-negative disease; AND
- **D)** The patient has *PIK3CA*-mutated breast cancer as detected by an approved test; AND
- **E)** The patient has progressed on or after at least one prior endocrine-based regimen; AND
  Note: Examples include anastrozole, letrozole, exemestane, tamoxifen, toremifene.
- **F)** Piqray will be used in combination with fulvestrant injection.

* Refer to Policy Statement

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Piqray has not been shown to be effective or there are limited or preliminary data that are not supportive of general approval for the following conditions.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

7. Piqray® tablets [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation.; May 2019.
8. Food and Drug Administration. Lists of cleared or approved companion diagnostic devices (in vitro and imaging tools). Available at: https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools. Accessed on May 21, 2019.
9. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 4.2020 – May 8, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 8, 2020.

HISTORY

Type of Revision	Summary of Changes*	Date Reviewed
New policy	--	05/29/2019
Selected revision	Added approval criteria for use of Piqray for breast cancer in premenopausal females based on guideline recommendations.	07/10/2019
Selected revision	Added criteria for Piqray use in combination with fulvestrant	10/02/2019
Annual revision	Changed gonadotropin releasing hormone "agonist" to "analog". Deleted fulvestrant from examples of prior endocrine therapy.	06/10/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Piqray® (alpelisib tablets – Novartis Pharmaceuticals Corporation)

DATE REVIEWED: 06/10/2020

OVERVIEW

Piqray is indicated in combination with fulvestrant injection for the treatment of postmenopausal women and men with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, phosphatidylinositol-3-kinase (*PIK3CA*)-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.[1] Patients treated with Piqray should have one or more *PIK3CA* mutations in tumor tissue or plasma specimens. If no mutation is detected in a plasma specimen, tumor tissue should be tested. Information on FDA-approved tests for the detection of *PIK3CA* mutations in breast cancer is available on the FDA website.[2]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on breast cancer (version 4.2020 – May 8, 2020) recommend Piqray, in combination with fulvestrant, as a preferred regimen (category 1) for *PIK3CA*-mutated tumors in postmenopausal or premenopausal patients (receiving ovarian ablation or suppression, if premenopausal) with HR+/HER2-negative, recurrent or Stage IV disease.[3] It is noted that the safety of Piqray in patients with Type 1 or uncontrolled Type 2 diabetes has not been established. Other preferred regimens for HR+/HER2-negative disease include the following: fulvestrant, aromatase inhibitor (i.e., letrozole, anastrozole, exemestane) + CDK4/6 inhibitor (i.e., Ibrance® [palbociclib capsules], Kisqali® [ribociclib tablets], Verzenio™ [abemaciclib tablets]), fulvestrant + CDK4/6 inhibitor (all category 1), aromatase inhibitor monotherapy, tamoxifen or toremifene, exemestane + Afinitor® (everolimus tablets), fulvestrant + Afinitor, and tamoxifen + Afinitor (all category 2A). Of note, men with breast cancer are treated similarly to postmenopausal women.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Piqray. All approvals are provided for the duration noted below. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: a woman is defined as an individual with the biological traits of a woman, regardless of the individual's gender identity or gender expression; men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Piqray is recommended in those who meet the following criteria:

FDA-Approved Indications

19. Breast Cancer. Approve for 3 years if the patient meets the following criteria (A, B, C, D, E, and F):

- **A)** The patient meets one of the following criteria (i or ii):
  - **i.** The patient is a postmenopausal female* or a male*; OR
  - **ii.** The patient is premenopausal* and is receiving ovarian suppression with a gonadotropin-releasing hormone (GnRH) analog or has had surgical bilateral oophorectomy or ovarian irradiation.

    Note: Examples include Lupron/Lupron Depot (leuprolide acetate injectable suspension), Trelstar (triptorelin pamoate injectable suspension), Zoladex (goserelin acetate implant); AND
- **B)** The patient has advanced or metastatic hormone receptor (HR)-positive disease; AND
- **C)** The patient has human epidermal growth factor receptor 2 (HER2)-negative disease; AND
- **D)** The patient has *PIK3CA*-mutated breast cancer as detected by an approved test; AND

E) The patient has progressed on or after at least one prior endocrine-based regimen; AND
Note: Examples include anastrozole, letrozole, exemestane, tamoxifen, toremifene.
F) Piqray will be used in combination with fulvestrant injection.

* Refer to Policy Statement

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Piqray has not been shown to be effective or there are limited or preliminary data that are not supportive of general approval for the following conditions.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

10. Piqray® tablets [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation.; May 2019.
11. Food and Drug Administration. Lists of cleared or approved companion diagnostic devices (in vitro and imaging tools). Available at: https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools. Accessed on May 21, 2019.
12. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 4.2020 – May 8, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 8, 2020.

HISTORY

Type of Revision	Summary of Changes*	Date Reviewed
New policy	--	05/29/2019
Selected revision	Added approval criteria for use of Piqray for breast cancer in premenopausal females based on guideline recommendations.	07/10/2019
Selected revision	Added criteria for Piqray use in combination with fulvestrant	10/02/2019
Annual revision	Changed gonadotropin releasing hormone "agonist" to "analog". Deleted fulvestrant from examples of prior endocrine therapy.	06/10/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Pomalyst Prior Authorization Policy
- Pomalyst® (pomalidomide capsules – Celgene)

REVIEW DATE: 04/01/2020; selected revision 05/27/2020

OVERVIEW

Pomalyst, a thalidomide analogue, is indicated for the treatment of multiple myeloma in combination with dexamethasone in adults who have received at least two prior therapies including Revlimid® (lenalidomide capsules) and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy.[1] Pomalyst is also indicated for the treatment of Acquired Immune Deficiency Syndrome (AIDS)-related Kaposi sarcoma in adults after failure of highly active antiretroviral therapy (HAART) or in patients with Kaposi sarcoma who are Human Immunodeficiency Virus (HIV)-negative.

Disease Overview

Multiple myeloma is a cancer formed by malignant plasma cells which are found in the bone marrow.[2] Normally, B cells responding to an infection change into plasma cells that make the antibodies to help the

body attack and kill pathogens. In multiple myeloma, these plasma cells grow out of control and become cancerous. Often, there are no symptoms of disease until it reaches an advanced stage. The most common signs and symptoms include: bone problems (e.g., pain, bone weakness, broken bones), decreased blood counts (e.g., anemia, leukopenia, thrombocytopenia), hypercalcemia, nervous system symptoms due to spinal cord compression, nerve damage, hyperviscosity, kidney problems, and infections. A monoclonal immunoglobulin (M protein) is produced by myeloma cells and may be found in the blood or excreted in the urine of patients with multiple myeloma. Beta-2 microglobulin is another protein made by myeloma cells, with high levels associated with more advanced disease.

Kaposi's sarcoma is a multifocal malignancy that impacts endothelial cells which manifest with red or brown papules.[3] The skin is the site most commonly involved, but the oral mucosa, lymph nodes, and viscera may also be impacted.[4] The risk of Kaposi's sarcoma is very high among patients who are HIV-positive but is also more common in other patient populations with altered cellular immunity (e.g., patients who have undergone transplants).[3,4] Kaposi's sarcoma is usually associated with human herpes virus 8 (HHV-8) infection.[3] In patients with Kaposi's sarcoma related to HIV, HAART is the foundation of therapy.[4] For patients who do not attain an adequate response with HAART, Kaposi's sarcoma-specific systemic therapies include liposomal anthracyclines (doxorubicin) and paclitaxel which have led to response rates between 46% to 76%.[4] Patients who are not HIV-positive have a less established treatment course but cytotoxics are used. Local therapies are also utilized for patients with limited disease (e.g., Panretin® [alitretinoin gel 0.1%], imiquimod 5%, intralesional chemotherapy with vinblastine).[3,4]

Clinical Efficacy
An open-label, single-center, single-arm clinical trial evaluated the efficacy of Pomalyst in patients with Kaposi'sarcoma.[4] Among the 28 patients, 18 patients were HIV-positive and 10 patients were HIV-negative. Patients received Pomalyst 5 mg once daily (QD) on Days 1 through 21 of each 28 day cycle until disease progression or unacceptable toxicity. All patients who were HIV-positive continued HAART. At the time of enrollment, 75% of patients had advanced disease and 75% of patients had previously received chemotherapy. The overall response rate among all patients was 71%; overall response rates were 67% and 80% among HIV-positive and HIV-negative patients, respectively. The time to first response was approximately 2 months. The duration of response was approximately 1 year.

Guidelines
The National Comprehensive Cancer Network (NCCN) guidelines on multiple myeloma (version 3.2020 – March 10, 2020) include Pomalyst.[5] Pomalyst is recommended in various clinical regimens in varying scenarios and with different agents among patients with multiple myeloma that has been previously treated. It can be used as a monotherapy for patients who are steroid-intolerant.

The NCCN has guidelines regarding AIDS-related Kaposi Sarcoma (version 1.2020 – February 12, 2020).[3] Pomalyst is cited as the preferred subsequent system therapy option for relapsed/refractory therapy. First-line systemic therapy options include liposomal doxorubicin (preferred) and paclitaxel. Of note, the clinical trial with Pomalyst used a dose of 5 mg QD. However, Pomalyst is provided as a 4 mg dose and the NCCN Panel believed that this dose is sufficient.

The NCCN has guidelines regarding Central Nervous System (CNS) Cancers (version 1.2020 – March 10, 2020).[6] Pomalyst is listed as a recommended regimen for patients with relapsed or refractory disease.

The NCCN has guidelines for systemic light chain amyloidosis (version 1.2020 – December 6, 2019).[7] The guidelines list Pomalyst plus dexamethasone as one of several treatment options for patients with previously treated disease.

Safety

Pomalyst has a Boxed Warning regarding embryofetal toxicity and venous arterial thromboembolism.[1] The availability of Pomalyst is through a restricted program called Pomalyst Risk Evaluation and Mitigation Strategy (REMS). Warnings and Precautions include hematologic toxicity, hepatotoxicity, hypersensitivity reactions, and tumor lysis syndrome.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Pomalyst. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Pomalyst is recommended in those who meet the following criteria:

FDA-Approved Indications

~~24.~~21. **Multiple Myeloma.** Approve for 3 years.

~~25.~~22. **Kaposi Sarcoma.** Approve for 3 years if the patient meets both of the following (A and B):
- **A)** The patient is ≥ 18 years of age; AND
- **B)** The patient meets one of the following (i or ii):
  - **i.** The patient is Human Immunodeficiency Virus (HIV)-negative; OR
  - **ii.** The patient meets both of the following (a and b):
    - **a)** The patient is Human Immunodeficiency Virus (HIV)-positive; AND
    - **b)** The patient continues to receive highly active antiretroviral therapy (HAART).

Other Uses with Supportive Evidence

~~26.~~23. **Central Nervous System (CNS) Lymphoma.** Approve for 3 years if the patient has relapsed or refractory disease.

~~27.~~24. **Systemic Light Chain Amyloidosis.** Approve for 3 years.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Pomalyst is not recommended in the following situations:

241. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

251. Pomalyst® capsules [prescribing information]. Summit, NJ: Celgene; May 2020.
252. American Cancer Society. Multiple myeloma. Last updated: February 28, 2018. Available at: http://www.cancer.org/cancer/multiplemyeloma/detailedguide/multiple-myeloma-key-statistics. Accessed on May 16, 2020.
253. The NCCN AIDS-Related Kaposi Sarcoma Clinical Practice Guidelines in Oncology (version 1.2020 – February 12, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 15, 2020.
254. Polizzotto MN, Uldrick TS, Wyvill KM, et al. Pomalidomide for symptomatic Kaposi's sarcoma in people with and without HIV infection: a Phase I/II study. *J Clin Oncol*. 2016;34(34):4125-4131.

255. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (Version 3.2020 – March 10, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 13, 2020.
256. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 1.2020 – March 13, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 13, 2020.
257. The NCCN Systemic Light Chain Amyloidosis Clinical Practice Guidelines in Oncology (Version 1.2020 – December 6, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 13, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early annual revision	No criteria changes.	03/07/2018
Annual revision	Criteria added to approve for patients with acquired immune deficiency syndrome-related Kaposi's sarcoma for 3 years if the patient has relapsed or refractory disease. Criteria added to approve for central nervous system lymphoma for 3 years if the patient has relapsed or refractory disease.	03/20/2019
Annual revision	The following changes were made: 1. **Myelofibrosis:** The condition (and related) criteria was removed as this agent is not recommended in related NCCN guidelines.	04/01/2020
Selected revision	The following changes were made: 1. **Kaposi's Sarcoma:** New criteria were added based on this newly FDA-approved indication for use. Approval is given for 3 years if the patient is greater or equal to 18 years of age if the patient is human immunodeficiency virus negative. For patients who are human immunodeficiency virus positive, the patient must be continuing to receive highly active antiretroviral therapy. 2. **Acquired Immunodeficiency Syndrome Related Kaposi's Sarcoma:** This indication that was listed in the "other uses with supportive evidence" section that approved for 3 years if the patient had relapsed or refractory diseases was removed. New criteria were developed based on its new FDA-approved indication of use.	05/27/2020

NCCN – National Comprehensive Cancer Network; FDA – Food and Drug Administration.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Qinlock™ (ripretinib tablets – Deciphera Pharmaceuticals, LLC)

REVIEW DATE: 05/20/2020

OVERVIEW

Qinlock, a kinase inhibitor, is indicated for the treatment of adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib. Qinlock inhibits KIT proto-oncogene receptor tyrosine kinase (KIT) and platelet derived growth factor receptor A (PDGFRA) kinase including wild type, primary, and secondary mutations.

Guidelines

According to the National Comprehensive Cancer Network (NCCN) soft tissue sarcoma guidelines (version 2.2020 – May 28, 2020), Qinlock is recommended as a "Preferred Regimen" for fourth-line therapy for unresectable or metastatic disease, after progressive disease on imatinib, Sutent (sunitinib tablets), and Stivarga (regorafenib tablets). Imatinib is a category 1 recommended option for primary treatment. Ayvakit™ (avapritinib tablets) is recommended first-line for platelet-derived growth factor receptor alpha (*PDGFRA*) exon 18 mutation, including *PDGFRA* D842V mutations. Upon disease progression on imatinib, Sutent is a category 1 recommended option. For disease progression on Sutent, Stivarga is the recommended option (category 1). Based on limited data, the guidelines recommend other small molecule inhibitors such as Nexavar® (sorafenib tablets), Votrient® (pazopanib tablets), Tasigna® (nilotinib tablets), Ayvakit, and everolimus + TKI (all category 2A) as "useful in certain circumstances" as fourth-line therapy for unresectable or metastatic disease.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Qinlock. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Qinlock is recommended in those who meet the following criteria:

FDA-Approved Indications

20. Gastrointestinal stromal tumor (GIST). Approve for 3 years if the patient meets the following criteria (A, B, and C):

A) The patient has advanced GIST; AND

B) The patient has been previously treated with imatinib; AND

C) The patient has been previously treated with at least two other kinase inhibitors, in addition to imatinib.

Note: Examples of kinase inhibitors are Sutent (sunitinib capsules), Stivarga (regorafenib tablets), Nexavar (sorafenib tablets), Votrient (pazopanib tablets), Tasigna (nilotinib capsules), Sprycel (dasatinib tablets).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Qinlock has not been shown to be effective or there are limited or preliminary data that are not supportive of general approval for the following conditions.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

13. Qinlock™ tablets [prescribing information]. Waltham, MA: Deciphera Pharmaceuticals, LLC; May 2020.
14. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (Version 1.2020 – May 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 15, 2020.

HISTORY

Type of Revision	Summary of Changes*	Date Reviewed
New policy	New criteria	05/20/2020
Update	6/18/2020: Updated guidelines	NA

NA – Not applicable.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Retevmo™ (selpercatinib capsules – Eli Lilly and Company)

DATE REVIEWED: 05/13/2020

OVERVIEW

Retevmo, a kinase inhibitor, is indicated for the treatment of:

1. Adult patients with metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC);[1]

2. Adult and pediatric patients ≥ 12 years of age with advanced or metastatic *RET*-mutant medullary thyroid cancer who require systemic therapy;

3. Adult and pediatric patients ≥ 12 years of age with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

Guidelines

Retevmo is not addressed in the guidelines. The National Comprehensive Cancer Network (NCCN) non-small cell lung cancer guidelines (version 3.2020 – February 11, 2020) recommend Cometriq (cabozantinib capsules) and Caprelsa (vandetanib tablets) for *RET* rearrangements.[2]

Retevmo is not addressed in the guidelines. The National Comprehensive Cancer Network (NCCN) thyroid carcinoma guidelines (version 2.2019 – September 16, 2019) recommend Cometriq (cabozantinib capsules) and Caprelsa (vandetanib tablets) for germline *RET* proto-oncogene mutations in locoregional, asymptomatic or symptomatic medullary carcinoma that is recurrent or persistent (both category 1, preferred).[3]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Retevmo. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Retevmo is recommended in those who meet the following criteria:

FDA-Approved Indications

1. Non-Small Cell Lung Cancer (NSCLC). Approve for 3 years if the patient meets the following criteria (A and B):

- **A)** The patient has metastatic disease; AND
- **B)** The tumor is *RET* fusion-positive.

2. Medullary Thyroid Cancer. Approve for 3 years if the patient meets the following criteria (A, B, and C):

Note: For other types of thyroid cancer see criteria below for "Thyroid Cancer".

- **A)** The patient is greater than or equal to 12 years of age; AND
- **B)** The patient has advanced or metastatic *RET*-mutant disease; AND
- **C)** The disease requires treatment with systemic therapy.

3. Thyroid Cancer. Approve for 3 years if the patient meets the following criteria (A, B, C, and D):

Note: For "Medullary Thyroid Cancer" see above criteria.

- **A)** The patient is greater than or equal to 12 years of age; AND
- **B)** That patient has advanced or metastatic *RET* fusion-positive disease; AND
- **C)** The disease is radioactive iodine-refractory (if radioactive iodine is appropriate); AND
- **D)** The disease requires treatment with systemic therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Retevmo has not been shown to be effective or there are limited or preliminary data that are not supportive of general approval for the following conditions.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

15. Retevmo™ capsules [prescribing information]. Indianapolis, IN: Eli Lilly and Company; May 2020.
16. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 3.2020 – February 11, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 10, 2020.
17. The NCCN Thyroid Cancer Clinical Practice Guidelines in Oncology (Version 2.2019 – September 16, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 10, 2020.

HISTORY

Type of Revision	Summary of Changes*	Date Reviewed
New policy	New criteria	05/13/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Revlimid Prior Authorization Policy

- Revlimid® (lenalidomide capsules – Celgene)

REVIEW DATE: 04/01/2020

OVERVIEW

Revlimid, a thalidomide analogue, is indicated in combination with dexamethasone for the treatment of patients with multiple myeloma.[1] It is also indicated as maintenance therapy in patients with multiple myeloma following autologous hematopoietic stem cell transplantation (auto-HSCT). Revlimid is also indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Revlimid is also indicated for the treatment of patients with mantle cell lymphoma whose disease has relapsed or progressed after two prior therapies, one of which included Velcade® (bortezomib injection). Revlimid is indicated in combination with a rituximab product for the treatment of adults with previously treated follicular lymphoma. Revlimid is indicated in combination with a rituximab product for the treatment of adults with previously-treated marginal zone lymphoma. A limitation of use with Revlimid is that it is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials.

Guidelines

The NCCN guidelines for acquired immune deficiency syndrome (AIDS)-Related Kaposi Sarcoma (version 1.2020 – February 12, 2020) recommended Revlimid as an Other Recommended Regimen for subsequent systemic therapy options for relapsed/refractory therapy.[2] First-line systemic therapy options include liposomal doxorubicin (preferred), and paclitaxel. Other subsequent systemic therapy options for relapsed/refractory therapy are also cited (e.g., Pomalyst® [pomalidomide capsules] {preferred}, Thalomid® [thalidomide capsules], imatinib).

The National Comprehensive Cancer Network (NCCN) guidelines for B-Cell Lymphomas (version 1.2020 – January 22, 2020) discuss therapeutic options for mantle cell lymphoma.[3] Revlimid, in combination with rituximab, is recommended as a preferred less-aggressive induction therapy (category 2A). Revlimid with or without rituximab is recommended as a preferred second-line therapy (Category 2A). Other recommended second line therapy regimens include Imbruvica, Revlimid, plus rituximab. The NCCN guidelines cited many treatments and medications regimens for mantle cell lymphoma in various clinical scenarios.

The NCCN guidelines for multiple myeloma (version 3.2020 – March 10, 2020) recommend Revlimid in a variety of scenarios.[4] Revlimid is use in various regimens and Revlimid combined with low-dose dexamethasone is cited as a Category 1 agent for primary therapy for non-transplant candidates. As a maintenance therapy, Revlimid also has a Category 1 recommendation. Revlimid, combined with other agents, is also part of a category 1 recommended therapy (preferred) for previously treated multiple myeloma.

The NCCN guidelines for MDS (version 2.2020 – February 28, 2020) recommend Revlimid in a variety of clinical scenarios among patients with symptomatic anemia both with and without 5q deletion abnormalities.[5]

The NCCN guidelines for B-Cell Lymphomas (version 1.2020 – January 22, 2020) recommend Revlimid as an option as subsequent therapy, with or without rituximab, for multi-centric Castleman's disease that has progressed after treatment of relapsed/refractory or progressive disease.[3]

NCCN guidelines for B-Cell Lymphomas (version 1.2020 – January 22, 2020) discuss therapeutic options for diffuse large B-cell lymphoma.[3] Revlimid, with or without rituximab, is mentioned as a second-line therapy. Many examples of first-line therapies are recommended (e.g., RCHOP [Rituximab cyclophosphamide, doxorubicin, vincristine, prednisone] {Category 1}, dose-adjusted EPOCH [etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin] + rituximab {Category 2A}). One examples of a first-line therapy for patients with poor left ventricular function or in those who are frail include RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine). NCCN also recommends optional first-line consolidation therapy of Revlimid maintenance (Category 2B) for patients aged 60 to 80 years.

NCCN guidelines for B-Cell Lymphomas (version 1.2020 – January 22, 2020) discuss therapeutic options for follicular lymphoma.[3] Revlimid plus rituximab is a first-line recommended therapy (Category 2A). Many second-line and subsequent therapies are listed, which include Revlimid, with or without rituximab.

The NCCN Hodgkin Lymphoma clinical practice guidelines (version 1.2020 – January 30, 2020) recommend Revlimid as an additional therapy option for treatment of classical Hodgkin lymphoma as a single agent for refractory or relapsed disease.[6]

The NCCN guidelines for B-Cell Lymphomas (version 1.2020 – January 22, 2020) discuss marginal zone lymphomas.[3] Revlimid plus rituximab has a Category 2B recommendation for first-line therapy. Revlimid with or without rituximab is also recommended as a second-line and subsequent therapy.

The NCCN has guidelines regarding myeloproliferative neoplasms (version 2.2019 – October 29, 2018) that discuss myelofibrosis with related anemia.[7] Revlimid is recommended, with or without prednisone, for patients with serum epoetin alfa levels > 500 mU/mL.

The NCCN guidelines for T-Cell Lymphomas (version 1.2020 – January 6, 2020) makes several recommendations that include Revlimid.[8] For peripheral T-cell lymphomas, Revlimid is recommended as second-line and subsequent therapy as a monotherapy. Similarily, Revlimid is recommended as a second-line and subsequent therapy for adult T-cell leukemia/lymphoma.

NCCN guidelines for systemic light chain amyloidosis (version 1.2020 – December 6, 2019) cite Revlimid as a therapeutic option used in combination with other agents in several clinical scenarios, including newly diagnosed disease.[9] The NCCN guidelines state that Phase II studies have noted that Revlimid in combination with dexamethasone is active in the treatment of patients with systemic light chain amyloidosis, including patients with relapsed/refractory disease.

The NCCN guidelines for Central Nervous System (CNS) Cancers (version 1.2020 – March 10, 2020) recommend Revlimid, with or without rituximab, as one of the options for patients with relapsed or refractory disease.[10]

Safety

In a prospective randomized clinical study in the first-line treatment of patients with CLL, use of Revlimid as a single agent increased the risk of death compared with chlorambucil given as a single agent.[1] The trial was stopped for safety in July 2013. In an interim analysis, 34 deaths occurred in 210 patients in the Revlimid treatment arm compared with 18 deaths among the 211 patients in the chlorambucil treatment arm (hazard ratio for overall survival was 1.92 [95% confidence interval {CI}: 1.08, 3.41]), which was consistent with a 92% increase in the risk of death. Also, serious adverse cardiovascular (CV) events, including atrial fibrillation, myocardial infarction, and cardiac failure, occurred more frequently in patients receiving Revlimid. Revlimid has a Boxed Warning regarding embryofetal toxicity, hematologic toxicity, and venous thromboembolism. Revlimid is only available through a restricted distribution program called the Revlimid Risk Evaluation Mitigation Strategy (REMS®). Males and females must follow the required reproductive precautions.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Revlimid. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Revlimid is recommended in those who meet the following criteria:

FDA-Approved Indications

~~28.~~25. **Follicular Lymphoma.** Approve for 3 years if the patient meets one of the following (A or B):

- **A)** The patient is using Revlimid in combination with rituximab; OR
- **B)** The patient has tried at least one prior therapy.
  Note: Examples include Treanda® (bendamustine injection) plus rituximab; Treanda plus Gazyva® (obinutuzumab injection for intravenous use); CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) plus Gazyva or rituximab; CVP (cyclophosphamide, vincristine, prednisone) plus Gazyva or rituximab; chlorambucil with or without rituximab; cyclophosphamide with or without rituximab; Gazyva; Copiktra™ (duvelisib capsules); Aliqopa® (copanlisib injection for intravenous use); or Zydelig® (idelalisib capsules).

~~29.~~26. **Mantle Cell Lymphoma**. Approve for 3 years.

~~30.~~27. **Marginal Zone Lymphoma.** Approve for 3 years.

~~31.~~28. **Multiple Myeloma.** Approve for 3 years.

~~32.~~29. **Myelodysplastic Syndrome (MDS).** Approve for 3 years if the patient meets ONE of the following (A, B, or C):

- **A)** The patient has symptomatic anemia; OR
- **B)** The patient has transfusion-dependent anemia; OR
- **C)** The patient has anemia that is not controlled with an erythroid stimulating agent (ESA) [e.g., Epogen®/Procrit® {epoetin alfa injection}, Aranesp® {darbepoetin alfa injection}].

Other Uses with Supportive Evidence

~~33.~~30. **Acquired Immune Deficiency Syndrome (AIDS)-Related Kaposi's Sarcoma.** Approve for 3 years if the patient meets the following (A and B):
A) The patient has tried at least one regimen or therapy; AND
B) The patient has relapsed or refractory disease.
Note: Examples include liposomal doxorubicin, paclitaxel, Pomalyst® (pomalidomide capsules), Thalomid® [thalidomide capsules], and imatinib.

~~34.~~31. **Castleman's Disease.** Approve for 3 years in patients with relapsed/refractory or progressive disease.

~~35.~~32. **Central Nervous System (CNS) Cancer (Primary).** Approve for 3 years if according to the prescriber the patient has relapsed or refractory disease.

~~36.~~33. **Diffuse, Large B Cell Lymphoma (DLBCL) [Non-Hodgkin's Lymphoma].** Approve for 3 years if the patient has tried at least one prior therapy.
Note: Examples include RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, predisone); dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab; RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine); DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab; ICE (Ifex, carboplatin, etoposide) ± rituximab; or Treanda ± rituximab.

~~37.~~34. **Hodgkin Lymphoma, Classical (nodular sclerosis, mixed cellularity, lymphocyte depleted, and lymphocyte-rich subtypes of Hodgkin lymphoma).** Approve for 3 years in patients with relapsed or refractory disease.

~~38.~~35. **Myelofibrosis.** Approve for 3 years if the patient meets the following criteria (A and B):
A) According to the prescriber the patient has anemia; AND
B) The patient has serum erythropoietin levels ≥ 500 mU/mL.

~~39.~~36. **Peripheral T-Cell Lymphomas.** Approve for 3 years if the patient has tried at least one other therapy or regimen.
Note: Examples of therapies or regimens include Beleodaq® (belinostat injection for intravenous infusion); Adcetris® (brentuximab vedotin injection for intravenous use); DHAP (dexamethasone, cisplatin, cytarabine); ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin); GDP (gemcitabine, dexamethasone, cisplatin); GemOX (gemcitabine, oxaliplatin); ICE (ifosfamide, carboplatin, etoposide); or Istodax® (romidepsin injection for intravenous infusion). Indications regarding peripheral T-cell lymphomas include peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL); enteropathy-associated T-cell lymphoma (EATL); monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL); nodal peripheral T-cell lymphoma (nodal PTCL) with TFH phenotype (TFH); follicular T-cell lymphoma (FTCL); and hepatosplenic gamma-delta T-cell lymphomas.

~~40.~~37. **Systemic Light Chain Amyloidosis.** Approve for 3 years.

~~41.~~38. **T-Cell Leukemia/Lymphoma.** Approve for 3 years if the patient has tried at least one other therapy or regimen.
Note: Examples include Adcetris® (brentuximab vedotin injection for intravenous use) plus CHP (cyclophosphamide, doxorubicin, and prednisone); CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone); CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone); dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin); HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone)

alternating with high-dose methotrexate and cytarabine; or Beleodaq® (belinostat injection for intravenous infusion).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Revlimid is not recommended in the following situations:

242. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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357. The NCCN Myeloproliferative Neoplasms Clinical Practice Guidelines in Oncology (Version 2.2019 – October 29, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 14, 2019.
358. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 1.2020 – January 6, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 13, 2020.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Added Venclexta as an option of agents that count as a trial for meeting the criteria for mantle cell lymphoma. Approval for marginal zone lymphoma was added. Added to approve for peripheral T-Cell Lymphomas and T-Cell leukemia/lymphoma if the patient has tried one other regimen.	03/20/2019
Selected Revision	1. Follicular Lymphoma: This condition was moved from Other Uses with Supportive Evidence to the Food and Drug Administration Approved Indications Section. In-line with the new labeling, the requirement was added that the patient is using Revlimid in combination with rituximab OR has tried one prior therapy with several examples provided in the policy. 2. Marginal Zone Lymphoma: This condition was moved from Other Uses with Supportive Evidence to the Food and Drug Administration Approved Indications Section. Criteria remain the same. 3. Mantle Cell Lymphoma: The requirement was removed that the patient had tried two prior regimens OR that the patient had tried one prior therapy or therapeutic regimen and cannot take Velcade according to the prescribing physician.	06/05/2019
Annual Revision	The following changes were made: 1. **Follicular Lymphoma:** The requirement that the patient has tried one prior therapy was changed to state "at least" and the examples of agents were moved from the criteria to a note. 2. **Acquired Immune Deficiency Kaposi's Sarcoma.** Criteria were added to approve if the patient has tried at least one regimen or therapy and the patient has relapsed or refractory disease. The examples of regimens are cited in a note. 3. **Central Nervous System Lymphoma (Primary)**: Criteria were added to approve for 3 years if the patient has relapsed or refractory disease. These were recommendations in NCCN guidelines. **4. Diffuse Large B-Cell Lymphoma:** The requirement that the patient has tried one other medication treatment regimen was changed to state "at least one prior therapy". Also, the examples of agents were moved from the criteria to a note. 5. **Myelofibrosis:** Criteria were revised to include that according to the prescriber the patient has anemia and that serum erythropoietin levels are ≥ 500 mU/mL. With the addition of this criteria, the requirement that the patient has tried one other therapy was removed. 6. **Peripheral T-Cell Lymphomas**: The requirement that the patient has one other chemotherapy regimen was changed to state "at least one other therapy or regimen." The examples of regimens/therapies were moved from the criteria to a note. Examples of Peripheral T-Cell Lymphomas were added as a note. 7. **T-Cell Leukemia/Lymphoma:** The requirement that the patient has one other chemotherapy regimen was changed to state "at least one other therapy or regimen." The examples of regimens/therapies were moved from the criteria to a note. 8. **Conditions Not Recommended for Approval**: The following conditions were deleted from this section: metastatic melanoma; metastatic renal cell carcinoma; ovarian carcinoma; and Waldenstrom macroglobulinemia.	04/01/2020

NCCN – National Comprehensive Cancer Network.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Rozlytrek Prior Authorization Policy

- Rozlytrek™ (entrectinib capsules – Genentech)

REVIEW DATE: 08/26/2020

OVERVIEW

Rozlytrek, a kinase inhibitor, is indicated for the following uses:[1]

- **Non-small cell lung cancer (NSCLC)**, for the treatment of adults with metastatic ROS1-positive disease.

- **Solid tumors**, treatment of adult and pediatric patients ≥ 12 years of age that a) have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion without a known acquired resistance mutation, b) are metastatic or where surgical resection is likely to result in severe morbidity, and c) have either progressed following treatment or have no satisfactory alternative therapy.

Guidelines

The National Comprehensive Cancer Network (NCCN) Compendium recommends the use of Rozlytrek for *NTRK* gene fusion-positive tumors in the following disease states:[2] pancreatic cancer, colon and rectal cancer, breast cancer, cutaneous melanoma, cervical cancer, squamous cell carcinoma, endometrial cancer, uterine sarcoma, several types of soft tissue sarcoma, hepatocellular/biliary tract/gallbladder carcinoma, brain metastases, NSCLC, ovarian cancer, salivary gland tumors, esophageal/esophagogastric junction cancers, gastric cancer, and thyroid cancer. It is also recommended for ROS1 rearrangement-positive NSCLC. Rozlytrek is a category 2A recommendation for most cancers.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Rozlytrek. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rozlytrek is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Solid Tumors.** Approve for 3 years if the patient meets the following criteria (A, B, C, and D):
   - **A)** Patient is ≥ 12 years of age; AND
   - **B)** Patient's tumor has neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation; AND
   - **C)** Patient meets one of the following criteria (i or ii):
     - **i.** The tumor is metastatic; OR
     - **ii.** Surgical resection of tumor will likely result in severe morbidity; AND
   - **D)** Patient meets one of the following criteria (i or ii):
     - **i.** Patient has progressed following treatment; OR
     - **ii.** There are no satisfactory alternative therapies.

2. **Non-Small Cell Lung Cancer.** Approve for 3 years if the patient has *ROS1*-positive metastatic disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rozlytrek is not recommended in the following situations:

243. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

361. Rozlytrek™ capsules [prescribing information]. South San Francisco, CA: Genetech; August 2019.

362. The NCCN Drugs & Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed August 24, 2020. Search terms: entrectinib.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	New criteria	08/16/2019
Update to New Policy	Updated criteria to match the FDA label	08/21/2019
Annual revision	No criteria changes	8/26/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Rubraca Prior Authorization Policy
- Rubraca™ (rucaparib tablets – Clovis Oncology)

REVIEW DATE: 03/10/2021

OVERVIEW

Rubraca, a poly (ADP-ribose) polymerase (PARP) inhibitor, is indicatedfor the following uses:[1]

- **Ovarian, fallopian tube, or primary peritoneal cancer**, for the **treatment** of adult patients with deleterious *BReast CAncer (BRCA)* mutation (germline and/or somatic) associated epithelial disease who have been treated with two or more chemotherapies.
- **Ovarian, fallopian tube, or primary peritoneal cancer,** for the **maintenance treatment** of adult patients with recurrent disease who are in a complete or partial response to platinum-based chemotherapy.
- **Prostate cancer, metastatic castration-resistant (mCRPC)**, treatment of adult patients with a deleterious *BRCA* mutation (germline and/or somatic)-associated disease who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy.

Guidelines

- **Ovarian Cancer:** According to the National Comprehensive Cancer Network (NCCN) guidelines for ovarian cancer (version 1. 2021 – February 26, 2021), therapy options for patients with recurrent disease are primarily dependent on whether the patient is considered platinum-resistant or platinum-sensitive (patients who relapse ≥ 6 months after initial chemotherapy).[3] NCCN Panel recommends single-agent Rubraca as recurrence therapy for patients with platinum-sensitive or platinum-resistant ovarian cancer that has been treated with two or more lines of chemotherapy and have *BRCA* mutations. The Panel feels that Rubraca is preferred for patients with platinum-resistant disease, because there are fewer good options for this setting. In patients with platinum-sensitive disease who have completed two or more lines of platinum-based therapy and are in a partial or complete response, bevacizumab can be continued as maintenance therapy; or Zejula™ (niraparib capsules), Lynparza™ (olaparib tablets), or Rubraca can be considered as maintenance therapy options (all category 2A).
- **Prostate Cancer:** The NCCN prostate cancer guidelines (version 2.2021 – February 17, 2021) recommend Rubraca for *BRCA1* or *BRCA2* mutation (germline and/or somatic) for its FDA-approved use in mCRPC, either as second-line or subsequent therapy (category 2A). It is listed under "useful in certain circumstances". The guidelines note that if the patient is not fit for chemotherapy, Rubraca can be considered even if taxane-based therapy has not been given.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Rubraca. All approvals are provided for 3 years in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rubraca is recommended in those who meet the following criteria:

FDA-Approved Indications

~~42.~~39. **Ovarian, Fallopian Tube, or Primary Peritoneal Cancer – Treatment.** Patient meets BOTH of the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets ONE of the following criteria (i or ii):
  - **i.** Initial Therapy. Approve for 3 years if the patient meets the following criteria (a and b):
    - **a)** Patient has a *BRCA*-mutation (germline or somatic) as confirmed by an approved test; AND
    - **b)** Patient has progressed on two or more prior lines of chemotherapy; OR
  - **ii.** Patient is Currently Receiving Rubraca. Approve for 3 years if the patient has a *BRCA* mutation (germline or somatic) as confirmed by an approved test.

2. **Ovarian, Fallopian Tube, or Primary Peritoneal Cancer –Maintenance Therapy.** Approve for 3 years if the patient meets the following criteria (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient is in complete or partial response after at least two platinum-based chemotherapy regimens. Note: Examples are carboplatin with gemcitabine, carboplatin with paclitaxel, cisplatin with gemcitabine.

3. **Prostate Cancer – Castration-Resistant.** Approve for 3 years if the patient meets the following criteria (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has metastatic disease that is *BRCA*-mutation positive (germline and/or somatic); AND
   - **C)** Patient meets one of the following criteria (i or ii):
     - **i.** The medication is used concurrently with a gonadotropin-releasing hormone (GnRH) analog; OR
       Note: Examples are Lupron (leuprolide for injection), Lupron Depot (leuprolide acetate for depot suspension), Trelstar (triptorelin pamoate for injectable suspension), Zoladex (goserelin acetate implant), Vantas (histrelin acetate subcutaneous implant), Firmagon (degarelix for injection).
     - **ii.** Patient has had a bilateral orchiectomy; AND
   - **D)** Patient has been previously treated with at least one androgen receptor-directed therapy; AND
     Note: Examples are abiraterone, Xtandi (enzalutamide tablets), Yonsa (abiraterone acetate tablets).
   - **E)** Patient meets one of the following criteria (i or ii):
     - **i.** Patient has been previously treated with at least one taxane-based chemotherapy; OR
       Note: Examples are docetaxel, cabazitaxel.
     - **ii.** Patient is not a candidate or is intolerant to taxane-based chemotherapy, according to the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rubraca is not recommended in the following situations:

244. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Modified Maintenance Therapy criteria in recurrent disease setting to state that it is after at least two lines of platinum-based chemotherapy, based on guidelines.	02/06/2019
Annual Revision	In Ovarian, Fallopian Tube, or Primary Peritoneal Cancer – Maintenance Therapy criteria, deleted criteria "the patient has recurrent disease."	02/19/2020
Selected Revision	Added new FDA-approved indication in prostate cancer.	05/27/2020
Annual Revision	**For all indications:** Added age requirement that patient ≥ 18 years.	03/10/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Rydapt Prior Authorization Policy
- Rydapt® (midostaurin capsules – Novartis)

REVIEW DATE: 02/10/2021

OVERVIEW

Rydapt, a tyrosine kinase inhibitor, is indicated in adults for the following uses:[1]
- **Acute myeloid leukemia (AML), newly diagnosed, that is FMS-like tyrosine kinase 3 (*FLT3*) mutation-positive** as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.
- **Aggressive systemic mastocytosis (AMS), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL)**.

AML

AML is a heterogeneous hematologic malignancy characterized by clonal expansion of myeloid blasts in the peripheral blood, bone marrow, and/or other tissues.[2] Undifferentiated blast cells proliferate in bone marrow instead of maturing into normal blood cells. Among adults, it is the most common form of acute leukemia and accounts for the largest number of annual deaths from leukemias in the US. An estimated 19,940 individuals will be diagnosed with AML in 2019 and 11,180 are projected to die from the condition. The median age at diagnosis is 67 years. Diagnosis occurs at ≥ 65 years of age for 54% of patients with around one-third of patients diagnosed at ≥ 75 years of age. The incidence of AML increase as the population ages. Environmental factors such as prolonged exposure to petrochemicals, solvents such as benzene, pesticides, and ionizing radiation have been established to increase the risks for AML, as well as myelodysplastic syndrome (MDS).[2] The cure rates of AML have improved with this outcome noted in 35% to 40% of adult patients who are ≤ 60 years of age and 5% to 15% for patients who are > 60 years of age.[3] However, among patients who are older and unable to receive intensive chemotherapy the survival rates are dismal with a median survival of only 5 to 10 months. Various gene mutations are present in adults with AML. The prognosis of AML is worse for patients with *FLT3* mutations which comprise approximately 30% to 40% of AML cases. Two major classes of activating *FLT3* mutations have been identified in patients with AML which include the ITD and TKD point mutations. *FLT3*/ITD mutations

occur in approximately 30% of cases and are more common than *FLT3*/TKD mutations, which occur in approximately 10% of patients.

Systemic Mastocytosis (SM)

Mastocytosis describes a rare group of disorders that are caused by too many mast cells in the body.[4-10] c-Kit mutations are implicated in some types of mastocytosis, including SM.[9] There are four major subtypes of SM: indolent SM (ISM), SM-AHN, ASM, and MCL.[8] The prognosis of ASM is highly variable, with a median survival of 3.5 to 7 years depending on the study. The only definitive therapy for ASM remains hematopoietic stem cell transplant (HSCT).[7] In general, the prognosis and treatment of SM-AHN is governed by the associated hematologic disorder while controlling the symptoms of mastocytosis. In SM-AHN, HSCT confers the greatest survival benefit in all forms of advanced SM, with a 3-year survival probability of 74% according to a large global retrospective study. The prognosis of SM-AHN remains poor, with a median survival estimated to be 2 to 4.4 years, depending on the study. MCL is by far the most aggressive form of SM, with median survival of approximately 6 months. HSCT offers a potentially curative role in appropriate patients with MCL, yet reports have failed to demonstrate reproducible evidence of durable eradication of the disease.

Guidelines

Various guidelines from the National Comprehensive Cancer Network (NCCN) address use of Rydapt.

- **Acute Myeloid Leukemia:** The NCCN guidelines on AML (version 2.2021 – November 12, 2020), recommend Rydapt + intravenous chemotherapy (e.g., cytarabine, daunorubicin) among the treatment options for induction, re-induction, and post-remission therapy.[3] It was noted that while Rydapt was not FDA-approved for maintenance therapy, the pivotal trial was designed for consolidation and maintenance Rydapt for a total of 12 months.
- **Myeloid/Lymphoid Neoplasms with Eosinophilia:** The NCCN guidelines myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase fusion genes (version 3.2021 – August 21, 2020) recommend Rydapt for patients with FGFR1 or FLT3 rearrangements in chronic phase.[11]
- **Systemic Mastocytosis:** In the NCCN has guidelines for systemic mastocytosis (version 1.2020 – May 21, 2020).[12] Rydapt is recommended for the treatment of aggressive systemic mastocytosis (category 2A), for the treatment of systemic mastocytosis with an associated hematologic neoplasm (category 2A), and for mast cell leukemia (category 2A).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Rydapt. Because of the specialized skills required for evaluation and diagnosis of patients treated with Rydapt approval requires Rydapt to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 3 years.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rydapt is recommended in those who meet the following criteria:

FDA-Approved Indications

~~43.~~40. **Acute Myeloid Leukemia (AML).** Approve for 3 years if the patient meets the following criteria (A B and C):

A) Patient is ≥ 18 years of age; AND

B) Patient is *FLT3*-mutation positive AML as detected by an approved test; AND

C) Patient is receiving Rydapt in one of the following settings (i, ii, iii, or iv):
- **i.** Induction therapy in combination with cytarabine and daunorubicin; OR
- **ii.** After standard-dose cytarabine induction/reinduction, along with cytarabine and daunorubicin; OR
- **iii.** Post remission or consolidation therapy in combination with cytarabine; OR
- **iv.** Maintenance therapy.

~~44.~~41. **Aggressive Systemic Mastocytosis (ASM).** Approve for 3 years if the patient is ≥ 18 years of age.

~~45.~~42. **Systemic Mastocytosis Associated with Acute Hematologic Neoplasm (SM-AHN).** Approve for 3 years if the patient is ≥ 18 years of age.

~~46.~~43. **Mast Cell Leukemia (MCL).** Approve for 3 years if the patient is ≥ 18 years of age.

Other Uses With Supportive Evidence

~~47.~~44. **Myeloid or Lymphoid Neoplasms with Eosinophilia.** Approve for 3 years if the patient meets one of the following (A or B):

A) Patient is ≥ 18 years of age; AND

B) Patient meets one of the following (i or ii):
- **i.** Patient has an FGFR1 rearrangement; OR
- **ii.** Patient has an FLT3 rearrangement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rydapt is not recommended in the following situations:

245. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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268. The NCCN Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes Clinical Practice Guidelines in Oncology (version 3.2021 – August 21, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 8, 2021.
269. The NCCN Systemic Mastocytosis Clinical Practice Guidelines in Oncology (version 1.2020 – May 21, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 8, 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes	07/11/2018
Early Annual Revision	The following changes were made: **Acute Myeloid Leukemia:** Criteria were added that the patient is receiving Rydapt in one of the following settings: 1) induction therapy in combination with cytarabine and daunorubicin; 2) after standard-dose cytarabine induction/reinduction, along with cytarabine and daunorubicin; 3) post-remission or consolidation therapy in combination with cytarabine; OR 4) maintenance therapy.	02/06/2019
Annual Revision	No criteria changes.	02/05/2020
Annual Revision	The following changes were made: **Acute Myeloid Leukemia:** Added criteria that the patient is ≥ 18 years of age. **Aggressive Systemic Mastocytosis:** Added criteria that the patient is ≥ 18 years of age. **Systemic Mastocytosis Associated with Acute Hematologic Neoplasm:** Added criteria that the patient is ≥ 18 years of age. **Mast Cell Leukemia:** Approve if the patient is ≥ 18 years of age. **Myeloid or Lymphoid Neoplasms with Eosinophilia:** Criteria were added based on guidelines to approve for 3 years if the patient has an FGFR1 rearrangement or an FLT3 rearrangement.	02/10/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Sprycel Prior Authorization Policy

- Sprycel® (dasatinib tablets – Bristol-Myers Squibb)

REVIEW DATE: 04/01/2020

OVERVIEW

Sprycel, a tyrosine kinase inhibitor (TKI), is indicated for the treatment of adults with: newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase (CP); chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib; and Ph+ acute lymphoblastic leukemia (ALL) with resistance or intolerance to prior therapy.[1] Additionally, Sprycel is indicated for the treatment of pediatric patients ≥ 1 year of age with Ph+ CML in CP and newly diagnosed Ph+ ALL in combination with chemotherapy. Currently, there are four other TKIs approved for the treatment of CP Ph+ CML: imatinib, Sprycel® (dasatinib tablets), Bosulif® (bosutinib tablets), Tasigna® (nilotinib capsules), and Iclusig® (ponatinib tablets).[2-5] These agents are indicated for the treatment of CP Ph+ CML in various phases; some TKIs are indicated after resistance or intolerance to prior therapy. Iclusig is approved for patients with T315I-positive CML and in adult patients with CML for whom no other TKI therapy is indicated.[5] Imatinib also has indications related to use in ALL.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for CML (version 3.2020 – January 30, 2020) state that for patients with CP CML with a low-risk score, the primary treatment recommended includes a first-generation TKI (Gleevec or generic imatinib 400 mg QD [Category 1]), or a second-generation TKI (Bosulif 400 mg QD [Category 1], Sprycel 100 mg QD [Category 1], or Tasigna 300 mg BID [Category 1]).[6] For patients with CP CML with an intermediate- or high-risk score, a second-generation TKI is preferred (Bosulif 400 mg QD [Category 1], Sprycel 100 mg QD [Category 1], or Tasigna 300 mg BID [Category 1]). A first-generation TKI (Gleevec or generic imatinib 400 mg QD) is an alternative [Category 2A]. Iclusig is an option for patients with a T315I mutation and for with disease that has not responded to multiple TKIs or in whom another TKI is not indicated.

The NCCN guidelines for ALL (version 1.2020 – January 15, 2020)[7] and Pediatric ALL (version 1.2020 – November 25, 2019)[8] recommend Sprycel in a variety of clinical scenarios including induction therapy, maintenance, relapsed or refractory ALL and for use in specific mutations.

The NCCN soft tissue sarcoma guidelines (version 6.2019 – February 10, 2020) indicate that Sprycel is a treatment option for patients with GIST as an additional option for patients who are no longer experiencing benefit from imatinib, Sutent® (sunitinib capsules), or Stivarga® (regorafenib tablets).[9] It is noted that data are limited with Sprycel (e.g., unpublished, Phase II, small numbers, retrospective). However, it was suggested that Sprycel may be a more effective option for patients with the D842V mutation.[8]

The NCCN guidelines on bone cancer (version 1.2020 – August 12, 2019) recommend Sprycel for patients with chondrosarcoma or chordoma.[10]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Sprycel. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sprycel is recommended in those who meet the following criteria:

FDA-Approved Indications

481. **Acute Lymphoblastic Leukemia (ALL) That is Philadelphia Chromosome Positive (Ph+).** Approve for 3 years.

482. **Chronic Myeloid Leukemia (CML) That is Philadelphia Chromosome Positive (Ph+).** Approve for 3 years.

Other Uses with Supportive Evidence

3. Gastrointestinal Stromal Tumor (GIST). Approve for 3 years if the patient meets the following criteria (A, B, and C):
- **A)** Patient has tried imatinb; AND
- **B)** Patient has tried Sutent® (sunitinib capsules); AND
- **C)** The patient has tried Stivarga® (regorafenib tablets).

4. Chondrosarcoma or chordoma. Approve for 3 years.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sprycel is not recommended in the following situations:

246. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

363. Sprycel® tablets [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; December 2018.
364. Gleevec® tablets [prescribing information]. East Hanover, NJ: Novartis; July 2018.
365. Tasigna® capsules [prescribing information]. East Hanover, NJ: Novartis; September 2019.
366. Bosulif® tablets [prescribing information]. New York, NY: Pfizer Inc; October 2019.
367. Iclusig® tablets [prescribing information]. Cambridge, MA: Ariad Pharmaceuticals; January 2020.
368. The NCCN Chronic Myeloid Leukemia Clinical Practice Guidelines in Oncology (Version 3.2020 – January 30, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 17, 2020.
369. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (Version 1.2020 – January 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 17, 2020.

370. The NCCN Pediatric Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (Version 2.2020 – November 25, 2019). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 17, 2020.
371. The NCCN Soft Tissue Sarcoma Practice Guidelines in Oncology (Version 6.2019 – February 10, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 17, 2020.
372. The NCCN Bone Cancer Clinical Practice Guidelines in Oncology (Version 1.2020 – August 12, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 17, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Removed the criteria allowing for approval if the patient has been started on Sprycel for an indication or condition addressed as an approval in the Recommended Authorization section (FDA-approved indication or other uses with supportive evidence section).	03/07/2018
Annual Revision	Approval is now given for patients with chordoma and chondrosarcoma for 3 years.	03/20/2019
Annual Revision	The following criteria changes were made: 1. **Conditions Not Recommended for Approval:** The following conditions were removed: breast cancer; chronic lymphocytic leukemia; colorectal cancer; head and neck squamous cell carcinoma; lung cancer; malignant mesothelioma; melanoma; non-small cell lung cancer; prostate cancer (metastatic, castration-resistant); and small cell lung cancer. These conditions are not recommended in the respective National Comprehensive Cancer Network (NCCN) guidelines and there has been a lack of recent literature regarding these uses.	04/01/2020

FDA – Food and Drug Administration.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Stivarga Prior Authorization Policy

- Stivarga® (regorafenib tablets – Bayer HealthCare Pharmaceuticals, Inc.)

REVIEW DATE: 01/20/2021

OVERVIEW

Stivarga, a kinase inhibitor, is indicated for the treatment of patients with the following conditions:[1]

1. **Colorectal cancer, metastatic** in patients who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor (VEGF) therapy, and, if *RAS* wild-type, an anti-epidermal growth factor receptor (EGFR) therapy.
2. **Gastrointestinal stromal tumor** (GIST), **locally advanced, unresectable or metastatic** in patients who have been previously treatment with imatinib mesylate (Gleevec®) and Sutent® (sunitinib malate capsules).
3. **Hepatocellular carcinoma** in patients who have been previously treated with Nexavar® (sorafenib tablets).

Guidelines

Stivarga is included in a number of National Comprehensive Cancer Network (NCCN) guidelines:

- **Bone cancer**: The NCCN guidelines (version 1.2021 – November 20, 2020) recommend Stivarga as a single agent for second-line therapy for relapsed/refractory or metastatic disease for patients with osteosarcoma (category 1), dedifferentiated chrondrosarcoma, and high-grade undifferentiated pleomorphic sarcoma (category 2B).[6,7]
- **Central nervous system cancers**: The NCCN guidelines on (version 3.2020 – September 11, 2020) recommend Stivarga as a single agent for the treatment of recurrent glioblastoma.[6,8]
- **Colon cancer and rectal cancer**: The NCCN guidelines on (version 1.2021 – December 22, 2020) and (version 1.2021 – December 22, 2020) recommend Stivarga as subsequent therapy as a single

agent for advanced or metastatic disease not previously treated with Stivarga in patients who have progressed through all available regimens except Stivarga or Lonsurf® (trifluridine and tipiracil tablets) with or without bevacizumab. Stivarga may be given before or after Lonsurf.[2,3,6]

- **Gastrointestinal stromal tumors**: The NCCN guidelines (version 1.2021 – September 12, 2019) recommend Stivarga (category 1) as a single agent for treatment of unresectable, recurrent, or metastatic GIST disease with widespread, systemic progression after single-agent therapy with Gleevec and Sutent.[6,9] Stivarga in combination with Afinitor® (everolimus tablets) is recommended for unresectable, recurrent, or metastatic disease after failure on approved therapies.
- **Hepatobiliary cancers**: The NCCN clinical practice guidelines on (version 5.2020 – August 4, 2020) recommend Stivarga for subsequent treatment as a single agent for patients with hepatocellular carcinoma (adenocarcinoma) [Child-Pugh Class A only] and disease progression for the following uses (all are category 1): 1) in patients who are not transplant candidates with unresectable disease, 2) in patients who are inoperable by performance status or comorbidity (local disease or local disease with minimal extrahepatic disease only), or in patients who have extensive liver tumor burden or metastatic disease.[5,6]
- **Soft tissue sarcoma**: The NCCN guidelines (version 1.2021 – October 30, 2020) recommend Stivarga (all category 2A) as single-agent subsequent therapy for patients with: 1) non-adipocytic extremity/body wall, head/neck sarcoma with advanced/metastatic disease with disseminated metastases, 2) non-adipocytic retroperitoneal/intra-abdominal sarcoma with recurrent unresectable or stage IV disease, 3) advanced/metastatic pleomorphic rhabdomyosarcoma, 4) angiosarcoma, or 5) solitary fibrous tumor.[4,6]

Safety

Stivarga has Boxed Warnings concerning risks of hepatotoxicity.[1] Hepatic function should be monitored prior to and during treatment.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Stivarga. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Stivarga is recommended in those who meet the following criteria:

FDA-Approved Indications

~~48.~~45. **Colon and Rectal Cancer.** Approve for 3 years if the patient meets all of the following criteria (A, B, C, D, and E):

17. Patient has advanced or metastatic disease; AND
18. Patient has been previously treated with a fluoropyrimidine (e.g., capecitabine, 5-fluorouracil [5-FU]); AND
19. Patient has been previously treated with oxaliplatin; AND
20. Patient has been previously treated with irinotecan; AND
21. If the patient's tumor or metastases are wild-type *RAS* (*KRAS* wild-type and/or *NRAS* wild-type) [that is, the tumors or metastases are *KRAS* and/or *NRAS* mutation negative], Erbitux (cetuximab injection for intravenous infusion) or Vectibix (panitumumab injection for intravenous infusion) has been tried.

2. Gastrointestinal Stromal Tumor (GIST). Approve for 3 years if the patient meets all of the following criteria (A, B, and C):

A) Patient has recurrent, metastatic, or unresectable disease; AND
B) Patient has been previously treated with imatinib ; AND

C) Patient has been previously treated with Sutent (sunitinib malate capsules).

3. **Hepatocellular Carcinoma.** Approve for 3 years if the patient has been previously treated with at least one tyrosine kinase inhibitor.
   Note: Tyrosine kinase inhibitors include Nexavar® (sorafenib tablets) and Lenvima® (lenvatinib capsules).

Other Uses with Supportive Evidence

4. **Glioblastoma.** Approve for 3 years if the patient has recurrent disease.

5. **Osteosarcoma.** Approve for 3 years if the patient meets both of the following criteria (A and B):
   A) Patient has relapsed/refractory or metastatic disease; AND
   B) Stivarga is used as subsequent therapy.

6. **Soft Tissue Sarcoma.** Approve for 3 years if the patient meets the following criteria (A and B):
   A) Patient has advanced or metastatic disease; AND
   B) Patient has one of the following (i, ii, iii, or iv):
      i. Non-adipocytic extremity/body wall, head/neck, or retroperitoneal/intra-abdominal sarcoma, OR
      ii. Pleomorphic rhabdomyosarcoma; OR
      iii. Angiosarcoma; OR
      iv. Solitary fibrous tumor.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Stivarga is not recommended in the following situations:

247. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Stivarga® tablets [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; June 2018.
2. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 1.2021 – December 22, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 14, 2021.
3. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (Version 1.2021 – December 22, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 14, 2021.
4. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (Version 1.2021 – October 30, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 15, 2021.
5. The NCCN Hepatobiliary Cancers Clinical Practice Guidelines in Oncology (Version 5.2020 – August 4, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 15, 2021.
6. The NCCN Drugs and Biologics Compendium. © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 14, 2021. Search term: regorafenib.
7. The NCCN Bone Cancer Clinical Practice Guidelines in Oncology (Version 1.2021 – November 20, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 14, 2021.
8. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (Version 3.2020 – September 11, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 14, 2021.
9. The NCCN Gastrointestinal Stromal Tumors Clinical Practice Guidelines in Oncology (Version 1.2021 – October 30, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on: January 14, 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Removed Other Uses with Supportive Evidence.	10/17/2018

Early Annual Revision	Hepatocellular carcinoma criteria revised to require use of at least one TKI prior to Stivarga. Prior criteria required Nexavar specifically. Criteria added for soft tissue sarcoma.	01/30/2019
Annual Revision	Criteria added for osteosarcoma Removed renal cell carcinoma from Conditions Not Recommended for Approval	01/29/2020
Annual Revision	**Colon and Rectal Cancer**: Added "advanced" to criteria, previous criteria stated Patient has metastatic disease. **Gastrointestinal Stromal Tumor**: Added "recurrent" to criteria, previous criteria stated Patient has metastatic or unresectable disease. **Glioblastoma**: Add criteria for glioblastoma. **Soft Tissue Sarcoma**: Added criteria for advanced or metastatic disease. Added angiosarcoma and solitary fibrous tumor to list of soft tissue sarcomas.	01/20/2021

TKI – Tyrosine kinase inhibitor.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Sutent® (sunitinib malate capsules – Pfizer)

DATE REVIEWED: 05/27/2020

OVERVIEW

Sutent, a multi-kinase inhibitor, is indicated for the treatment of gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate (Gleevec® tablets, generics); for the treatment of advanced renal cell carcinoma (RCC); for the adjuvant treatment of adult patients at high risk of recurrent RCC following nephrectomy; and for the treatment of progressive, well-differentiated pancreatic neuroendocrine tumors (PNET) in patients with unresectable locally advanced or metastatic disease.[1]

Guidelines

Sutent features prominently in the National Comprehensive Cancer Network (NCCN) compendium for all of the indications listed in the FDA-approved and Other Uses with Supportive Evidence.[2]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Sutent. All approvals are provided for 3 years in duration.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sutent is recommended in those who meet the following criteria:

FDA-Approved Indications

15. **Gastrointestinal Stromal Tumor (GIST).** Approve for 3 years if the patient has tried imatinib (Gleevec tablets, generics).

~~49.~~46. **Renal Cell Carcinoma (RCC) –Clear Cell or Non-Clear Cell Histology.** Approve for 3 years if the patient meets ONE of the following criteria (A or B):
   - **A)** The patient is at high risk of recurrent clear cell RCC following nephrectomy and Sutent is used for adjuvant therapy; OR

B) The patient has relapsed or Stage IV disease.

3. Neuroendocrine Tumors of the Pancreas. Approve for 3 years for advanced or metastatic disease.

Other Uses with Supportive Evidence

4. Alveolar Soft Part Sarcoma (ASPS). Approve for 3 years.

5. Angiosarcoma. Approve for 3 years.

6. Chordoma. Approve for 3 years in patients with recurrent disease.

7. Differentiated (i.e., papillary, follicular, and Hürthle cell) Thyroid Carcinoma. Approve for 3 years if refractory to radioactive iodine therapy.

8. Medullary Thyroid Carcinoma. Approve for 3 years if the patient has tried Caprelsa® (vandetanib tablets) or Cometriq® (cabozantinib capsules).

9. Meningioma. Approve for 3 years if the patient has recurrent or progressive disease.

10. Solitary Fibrous Tumor/Hemangiopericytoma. Approve for 3 years.

11. Thymic Carcinoma. Approve for 3 years if the patient has tried chemotherapy (e.g., carboplatin/paclitaxel) or radiation therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Sutent has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below.

248. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

373. Sutent® capsules [prescribing information]. New York, NY: Pfizer; May 2019.
374. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 25, 2020. Search term: sunitinib.

HISTORY

Type of Revision	Summary of Changes*	Date Reviewed
Selected revision	Renal Cell Carcinoma: Added criteria for approval in patients post-nephrectomy for adjuvant Sutent therapy based on FDA-approved new indication.	12/06/2017
Annual revision	Gastrointestinal Stromal Tumor: Added criteria for combination of Sutent with Afinitor.	04/11/2018
Annual revision	• Gastrointestinal Stromal Tumors (GIST): Deleted Sutent "is used as a single agent". Deleted criteria for combination therapy with Afinitor since this is covered in the Afinitor PA policy. • Renal Cell Carcinoma: Deleted "advanced" as qualifier; instead added criteria patient has relapsed or Stage IV disease as per guidelines. Deleted"predominant" in reference to clear cell histology in line with guidelines.	05/08/2019

	• Neuroendocrine Tumors of the Pancrease: Added "of the Pancreas" to condition description. Deleted "Advanced or Unresectable". Instead added "advanced or metastatic disease" in criteria. • Deleted all of the 17 conditions listed under "Conditions not Recommended for Approval".	
Annual revision	• No criteria changes	05/27/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Tabrecta™ (capmatinib tablets – Novartis.)

DATE REVIEWED: 05/11/2020

OVERVIEW

Tabrecta, a kinase inhibitor, is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as detected by an FDA-approved test.[1]

Guidelines

Tabrecta is not addressed in the guidelines. The National Comprehensive Cancer Network (NCCN) non-small cell lung cancer guidelines (version 3.2020 – February 11, 2020) recommend Xalkori (crizotinib capsules) in patients with high-level *MET* amplification or *MET* exon 14 skipping mutation (category 2A).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Tabrecta. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tabrecta is recommended in those who meet the following criteria:

FDA-Approved Indications

483. **Non-Small Cell Lung Cancer (NSCLC).** Approve for 3 years if the patient meets the following criteria (A and B):
   A) The patient has metastatic disease; AND
   B) The tumor is positive for a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping, as detected by an approved test.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Tabrecta has not been shown to be effective or there are limited or preliminary data that are not supportive of general approval for the following conditions.

7. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

18. Tabrecta™ tablets [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; May 2020.
19. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 3.2020 – February 11, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 11, 2020.

HISTORY

Type of Revision	Summary of Changes*	Date Reviewed
New policy	New criteria	05/11/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Tafinlar Prior Authorization Policy
- Tafinlar® (dabrafenib capsules – GlaxoSmithKline)

REVIEW DATE: 07/15/2020

OVERVIEW

Tafinlar, a BRAF inhibitor, is indicated for the following uses:[1]

- **Melanoma**, in the following situations:[1]
  - As a single agent for the treatment of patients with unresectable or metastatic disease with *BRAF V600E* mutation as detected by an FDA-approved test; AND
  - In combination with Mekinist® (trametinib tablets), for the treatment of patients with unresectable or metastatic disease with *BRAF V600E* or *V600K* mutations as detected by an FDA-approved test; AND
  - As adjuvant treatment of *BRAF V600E* or *V600K* mutation-positive disease as detected by an FDA-approved test, and involvement of the lymph node(s), following complete resection.
- **Non-small cell lung cancer**, in combination with Mekinist for treatment of disease that has the *BRAF V600E* mutation as detected by an FDA-approved test.
- **Thyroid cancer**, in combination with Mekinist, for treatment of patients with locally advanced or metastatic anaplastic disease with *BRAF V600E* mutation and with no satisfactory locoregional treatment options.

Tafinlar is not indicated for the treatment of patients with wild-type BRAF disease.

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines support use of Tafinlar in multiple cancers.

- **Melanoma:** Guidelines (version 3.2020 – May 18, 2020) recommend BRAF/MEK inhibitor combinations for first-line (preferred if clinically needed for early response) and subsequent treatment of metastatic or unresectable melanoma with a *V600* activating mutation.[2] While combination BRAF/MEK inhibition is preferred, if a combination is contraindicated, monotherapy with a BRAF inhibitor (Tafinlar or Zelboraf® [vemurafenib tablets]) is a recommended option, particularly if the patient is not a candidate for checkpoint immunotherapy. Following resection of limited metastatic disease with a *BRAF V600*-activating mutation, BRAF/MEK combination therapy is among the treatment options for patients with no evidence of disease. Tafinlar + Mekinist is also recommended in guidelines as adjuvant therapy (including for nodal recurrence) in some patients with Stage III disease, including use post-surgery or use after complete lymph node dissection. If unacceptable toxicity to Tafinlar/Mekinist, other BRAF/MEK combinations can be considered.

- **Non-Small Cell Lung Cancer:** Guidelines (version 6.2020 – June 25, 2020) list Tafinlar + Mekinist among the first-line therapy and subsequent therapy options for tumors with a *BRAF* mutation.[3] NCCN also notes that monotherapy with a BRAF inhibitor (Tafinlar or Zelboraf) is a treatment option when combination therapy is not tolerated.
- **Thyroid Cancer:** Guidelines (version 1.2020 – June 12, 2020) list Tafinlar + Mekinist as a treatment option for metastatic anaplastic thyroid cancer with a *BRAF* mutation.[4] Tafinlar and Zelboraf are also treatment options for the treatment of iodine-refractory differentiated thyroid cancer (follicular, Hürthle cell, and papillary cancer subtypes) with a *BRAF V600* mutation.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Tafinlar. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tafinlar is recommended in those who meet the following criteria:

FDA-Approved Indications

3. Melanoma. Approve for 3 years if the patient meets BOTH of the following (A and B):
- **A)** Patient has unresectable, advanced (including Stage III or Stage IV disease), or metastatic melanoma; AND
  Note: This includes adjuvant treatment in patients with Stage III disease with no evidence of disease post-surgery.
- **B)** Patient has *BRAF V600* mutation-positive disease.

4. Non-Small Cell Lung Cancer. Approve for 3 years if the patient has *BRAF V600E* mutation-positive disease.

5. Thyroid Cancer, Anaplastic. Approve for 3 years if the patient meets ALL of the following (A, B, and C):
- **D)** Patient has locally advanced or metastatic anaplastic disease; AND
- **E)** Tafinlar will be taken in combination with Mekinist, unless intolerant; AND
- **F)** Patient has *BRAF V600* mutation-positive disease.

Other Uses with Supportive Evidence

6. Thyroid Cancer, Differentiated. Approve for 3 years if the patient meets ALL of the following conditions (A, B, and C):
- **A)** Patient has differentiated thyroid carcinoma; AND
  Note: Examples of differentiated thyroid carcinoma include papillary, follicular, or Hürthle cell thyroid cancers.
- **B)** Patient has disease that is refractory to radioactive iodine therapy; AND
- **C)** Patient has *BRAF* mutation-positive disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tafinlar is not recommended in the following situations:

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

319. Tafinlar® capsules [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; April 2020.
320. The NCCN Melanoma Clinical Practice Guidelines in Oncology (Version 3.2020 – May 18, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 2, 2020.
321. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 6.2020 – June 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 2, 2020.
322. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (Version 1.2020 – June 12, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 2, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early annual revision	Add criteria to approve for 3 years for locally advanced or metastatic anaplastic thyroid cancer that is BRAF V600-positive, if taken in combination with Mekinist (unless intolerant). Due to new indication as adjuvant therapy in resectable melanoma, remove criteria that does not allow coverage in patients who had disease progression while on a BRAF inhibitor. Remove continuation criteria in melanoma; now all approvals require that the patient has unresectable, advanced (including Stage III or Stage IV disease), or metastatic melanoma with a BRAF mutation. In Other Uses with Supportive Evidence, add criteria to approve for 3 years for differentiated thyroid cancer, if BRAF-positive and refractory to radioactive iodine therapy.	05/23/2018
Annual revision	**NSCLC:** The diagnosis was changed to remove the BRAF mutation from the approval condition. The requirement that the patient has BRAF V600E mutation was added to the criteria for patients with NSCLC. **Colon or Rectal Cancer:** Add criteria as supported by NCCN colon cancer guidelines. Criteria approve if the patient has *BRAF V600E* mutation-positive disease, and if the patient has previously used chemotherapy, and if the agent will be used as part of a combination regimen for colon or rectal cancer.	06/18/2019
Annual revision	**Colon or Rectal Cancer:** This indication was removed from the policy. Tafinlar is no longer a recommended therapy in guidelines for colon and rectal cancer.	07/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Tagrisso Prior Authorization Policy

- Tagrisso® (osimertinib tablets – AstraZeneca)

REVIEW DATE: 01/06/2021

OVERVIEW

Tagrisso, a kinase inhibitor, is indicated for the treatment of adult patients for the following uses:[1]

- **Non-small cell lung cancer (NSCLC)**, with metastatic epidermal growth factor receptor (*EGFR*) T790M mutation-positive disease, as detected by an FDA-approved test. It is specifically approved for patients who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy (EGFR-TKI).
- **NSCLC**, first-line treatment of patients with metastatic NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.
- **NSCLC**, adjuvant therapy after tumor resection in tumors that have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for NSCLC (version 2.2021 – December 15, 2020) recommend *EGFR* mutation testing in patients with nonsquamous NSCLC (i.e., adenocarcinoma, large cell, NSCLC not otherwise specified [NOS]) and squamous cell NSCLC.[2] Tagrisso is recommended for consideration in patients who have been treated with previous adjuvant chemotherapy or ineligible for platinum-based chemotherapy in stage IB-IIIA *EGFR* mutation-positive disease after complete resection (category 2A). For advanced or metastatic disease, erlotinib, Iressa® (gefitinib tablets), Gilotrif™ (afatinib tablets), Vizimpro® (dacomitinib tablets), and Tagrisso (all category 1) are all recommended for the first-line treatment of patients with sensitizing *EGFR*-mutation positive NSCLC. Tagrisso is noted as the "preferred" first-line option by NCCN. Upon disease progression, T790M testing is recommended in guidelines. For systemic multiple lesions that are T790M mutation-positive, Tagrisso, if not previously given, is the category 1 recommended option. If T790M mutation-negative, initial cytotoxic therapy options listed for adenocarcinoma, or squamous cell carcinoma (e.g., doublet chemotherapy) can be considered in this setting (category 2A). NCCN notes that in patients with actionable mutations. Immunotherapy is less effective in the second-line setting, irrespective of PD-L1 expression.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tagrisso. All approvals are provided for 3 years in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tagrisso is recommended in those who meet the following criteria:

FDA-Approved Indications

~~50.~~47. **Non-Small Cell Lung Cancer (NSCLC) – Epidermal Growth Factor Receptor (*EGFR*) Mutation-Positive.** Approve if the patient meets the following criteria (A and B):

A) Patient is ≥ 18 years of age; AND

B) Patient meets ONE of the following criteria (i, ii, or iii):

i. Approve for up to 3 years (total) if the patient meets BOTH of the following criteria (a and b):

a) The medication is used as adjuvant therapy after tumor resection; AND

b) The tumor is positive for *EGFR* exon 19 deletions or exon 21 L858R mutations, as detected by an approved test; OR

ii. Approve for 3 years if the patient meets BOTH of the following criteria (a and b):

a) Patient has metastatic *EGFR* T790M mutation-positive NSCLC as detected by an approved test; AND

b) Patient has progressed on one of the EGFR-tyrosine kinase inhibitors; OR
Note: Examples are erlotinib , Iressa® [gefitinib tablets], Vizimpro® [dacomitinib tablets], Gilotrif® [afatinib tablets]; OR

iii. Approve for 3 years if the patient meets ONE of the following criteria (a or b):

a) Patient has metastatic disease with *EGFR* exon 19 deletions as detected by an approved test; OR

b) Patient has metastatic disease with *EGFR* exon 21 L858R mutations as detected by an approved test.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tagrisso is not recommended in the following situations:

249. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

323. Tagrisso™ tablets [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; December 2020.
324. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 2.2021 – December 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 23, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Selected Revision	Moved approval criteria for use in first-line setting for exon 19 or exon 21 mutations to under FDA-approved use due to new indication approval. Deleted "advanced or" from first-line setting use.	04/25/2018
Annual Revision	Criteria modified for T790M mutation where the list of agents is replaced with "one of the EGFR-tyrosine kinase inhibitors". The agents are listed as examples. Vizimpro was added to this list.	12/19/2018
Annual Revision	No criteria changes.	12/18/2019
Annual Revision	**Non-Small Cell Lung Cancer:** Added age requirement. Added new approval criteria for up to 3 years for Tagrisso use as adjuvant therapy based on FDA-approval. Moved examples of EGFR tyrosine kinase inhibitors to Note.	01/06/2021

EGFR – Epidermal growth factor receptor.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Talzenna Prior Authorization Policy
- Talzenna™ (talazoparib capsules – Pfizer)

REVIEW DATE: 11/11/2020

OVERVIEW
Talzenna, a poly (ADP-ribose) polymerase (PARP) inhibitor, is indicated in adult patients with deleterious or suspected deleterious germline BReast CAncer susceptibility gene **(g*BRCA*)-mutated** human epidermal growth factor receptor 2 **(HER2)-negative locally-advanced or metastatic breast cancer**.[1]

GUIDELINES
The National Comprehensive Cancer Network (NCCN) guidelines on breast cancer (version 6.2020 – September 8, 2020) recommends Talzenna as a category 1 preferred regimen for patients with recurrent or metastatic breast cancer which are HER2-negative and have germline *BRCA*1/2 mutation.[2] Lynparza® (olaparib tablets) is another category 1 recommended option in this setting. The guidelines note that although Talzenna and Lynparza are FDA-approved for HER2-negative disease, the NCCN Panel supports use of these agents in any subtype associated with a germline *BRCA1* or *BRCA2* mutation.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Talzenna. All approvals are provided for 3 years in duration.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Talzenna is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Breast Cancer.** Approve for 3 years if the patient meets the following criteria (A, B, and C):
   - **A.** Patient has locally-advanced or metastatic breast cancer; AND
   - **B.** Patients has germline *BRCA* mutation-positive disease; AND
   - **C.** Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Talzenna is not recommended in the following situations:

250. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

325. Talzenna™ capsules [prescribing information]. New York, NY: Pfizer; March 2020.
326. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 6.2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on November 9, 2020.

HISTORY
Type of Revision	Summary of Changes	Review Date

New Policy	New Policy	10/24/2018
Annual Revision	No criteria changes	10/30/2019
Annual Revision	No criteria changes	11/11/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Targretin (Oral) Prior Authorization Policy
- Targretin (bexarotene capsule – Bausch Health, generics)

REVIEW DATE: 09/30/2020

OVERVIEW
Bexarotene capsule is indicated for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy.[1] Bexarotene capsule has a Boxed Warning about birth defects and bexarotene must not be administered to a pregnant patient.

Disease Overview
CTCL is one of the most common form of T-cell lymphoma.[2,3] The most common type of cutaneous T-cell lymphoma is mycosis fungoides, which accounts for approximately 50% of all cutaneous T-cell lymphomas.[2] Skin symptoms associated with mycosis fungoides include patches, plaques, or tumors and treatment is directed at the skin or the entire body (systemic).[2,3] Sézary syndrome is an advanced, variant form of mycosis fungoides and is characterized by the presence of lymphoma cells in the blood. Patients with Sézary syndrome will have extensive thin, red, itchy rashes usually covering over 80% of the body and treatment will generally include systemic therapies since the use of skin- directed therapies alone is typically inadequate. Skin-directed therapies are useful for patch and limited plaque disease. Systemic therapies are reserved for more advanced disease and initiation of systemic therapy is usually deferred until patients have not responded to topical therapies.

Guidelines
The National Comprehensive Cancer Network (NCCN) guidelines on Primary Cutaneous Lymphomas (version 2.2020 – April 10, 2020) provide treatment recommendations for the different types of cutaneous T-cell lymphomas.[2] Bexarotene capsules are listed as one of the therapies within the Systemic Category A drugs. The Systemic Category A drugs are used before Systemic Category B drugs.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of bexarotene capsules. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with bexarotene capsules as well as the monitoring required for adverse events, approval requires bexarotene capsules to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of bexarotene capsules as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of bexarotene capsule is recommended in those who meet the following criteria:

FDA-Approved Indications

~~51.~~48. **Cutaneous T-Cell Lymphoma – Cutaneous Manifestations**. Approve bexarotene capsule for 3 years if the patient meets the following criteria (A and B):

Z) The medication is prescribed by or in consultation with an oncologist or a dermatologist; AND

AA) If brand Targretin is requested, the patient has tried AND cannot take generic bexarotene capsules due to a formulation difference in the inactive ingredient(s) (e.g., difference in dyes, fillers, preservatives) between the brand and the bioequivalent generic product which, per the prescribing physician, would result in a significant allergy or a serious adverse reaction **[documentation required]**.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of bexarotene capsules is not recommended in the following situations:

251. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

375. Targretin® capsule [prescribing information]. Bridgewater, NJ: Bausch Health US, LLC; April 2020.
376. Cutaneous T-cell lymphoma fact sheet. Available at: http://www.lymphoma.org/site/pp.asp?c=bkLTKaOQLmK8E&b=6300151. Accessed on September 23, 2020.
377. The NCCN Primary Cutaneous Lymphomas Clinical Practice Guidelines in Oncology (Version 2.2020 – April 10, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 23, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Add Poteligeo® (mogamulizumab-kpkc injection) to the list of products in the Note regarding an exception to the requirement for a trial of an oral retinoid, methotrexate, or phototherapy.	09/05/2018
Annual Revision	• Initial Therapy • Removed the criteria: The patient has tried ONE oral retinoid (tretinoin capsules, isotretinoin capsules [Amnesteem®, Claravis™, generics], acitretin capsules [Soriatane®, generics]), methotrexate, or phototherapy. (NOTE: An exception to the requirement for a trial of an oral retinoid, methotrexate, or phototherapy can be made if the patient has already used one of the following: interferons, histone deacetylase [HDAC] inhibitors, extracorporeal photopheresis, Poteligeo® (mogamulizumab-kpkc injection). These patients are not required to "step back" and try an oral retinoid, methotrexate, or phototherapy). • Removed the criterion: The patient has a type of CTCL (e.g., folliculotropic disease, advanced disease) that according to the prescribing physician, requires treatment with oral bexarotene capsules. • With the removal of the above two criteria, the criteria for "Initial Therapy" and for "Patient is currently receiving bexarotene capsule (Targretin, generics) or has received bexarotene capsules in the past" are identical and therefore, the criteria will not distinguish between "Initial Therapy" and "Patient is currently receiving bexarotene capsule (Targretin, generics) or has received bexarotene capsules in the past" (i.e., there will only be one set of criteria).	09/25/2019
Annual Revision	No criteria changes.	09/30/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Targretin (Topical) Prior Authorization Policy
- Targetin® (bexarotene gel 1% - Valeant)

REVIEW DATE: 09/30/2020

OVERVIEW

Targetin gel is indicated for the topical treatment of cutaneous lesions in patients with cutaneous T-cell lymphoma (Stage 1A and 1B) who have refractory or persistent disease after other therapies or who have not tolerated other therapies.[1] Targretin gel is contraindicated in pregnant patients and it should not be given to a pregnant patient or a patient who intends to become pregnant. If a patient becomes pregnant while using Targetin gel, it must be discontinued immediately.

Disease Overview

Cutaneous T-cell lymphoma is one of the most common forms of T-cell lymphoma.[2,3] The most common type of cutaneous T-cell lymphoma is mycosis fungoides, which accounts for approximately 50% of all cutaneous T-cell lymphomas.[2] Skin symptoms associated with mycosis fungoides include patches, plaques, or tumors and treatment is directed at the skin or the entire body (systemic).[2,3] Sézary syndrome is an advanced, variant form of mycosis fungoides and is characterized by the presence of lymphoma cells in the blood. Patients with Sézary syndrome will have extensive thin, red, itchy rashes usually covering over 80% of the body and treatment will generally include systemic therapies since the use of skin- directed therapies alone is typically inadequate. Skin-directed therapies are useful for patch and limited plaque disease. Systemic therapies are reserved for more advanced disease and initiation of systemic therapy is usually deferred until patients have not responded well to topical therapies.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on Primary Cutaneous Lymphomas (version .2020 – April 10, 2020) provide treatment recommendations for the different types of cutaneous T-cell lymphomas.[2] Targretin gel is listed as an option for skin-directed therapies (as initial therapy and for patients who have tried other skin-directed therapies).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Targretin gel. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Targretin gel as well as the monitoring required for adverse events and long-term efficacy, approval requires Targretin gel to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Targretin gel is recommended in those who meet the following criteria:

FDA-Approved Indications

~~52.~~49. **Cutaneous T-Cell Lymphoma – Cutaneous Manifestations.** Approve Targretin gel for 3 years if Targretin is prescribed by or in consultation with an oncologist or a dermatologist

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Targretin gel is not recommended in the following situations:

252. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

378. Targretin® gel [prescribing information]. Bridgewater, NJ: Bausch Health US, LLC; February 2020.
379. Cutaneous T-cell lymphoma fact sheet. Available at: http://www.lymphoma.org/site/pp.asp?c=bkLTKaOQLmK8E&b=6300151. Accessed on September 23, 2020.
380. The NCCN Primary Cutaneous Lymphomas Clinical Practice Guidelines in Oncology (Version 2.2020 – April 10, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 23, 2020.
381. Kinney MC, Jones D. Cutaneous T-cell and natural killer (NK)-cell lymphomas. The World Health Organization (WHO) and European Organization for Research and Treatment of Cancer (EORTC) classification and the increasing recognition of specialized tumor types. *Am J Clin Pathol*. 2007;127:670-686.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Add Poteligeo® (mogamulizumab-kpkc injection) to the list of products in the Note regarding an exception to the requirement for a trial of a topical corticosteroid and topical imiquimod.	09/05/2018
Annual Revision	• Removed the criterion for Initial Therapy: The patient has tried a topical corticosteroid and topical imiquimod cream (Aldara®, generics; Zyclara®). (NOTE: An exception to the requirement for a trial of a topical corticosteroid and topical imiquimod cream can be made if the patient has already used one of the following: another skin-directed therapy, e.g., topical chemotherapy, topical	9/25/2019

	retinoids, local radiation, phototherapy [UVB, NB-UVB, PUVA], TSEBT; or a systemic therapy, e.g., oral retinoids, interferons, histone deacetylase [HDAC] inhibitors, extracorporeal photopheresis, methotrexate, systemic chemotherapeutic agents, Poteligeo® (mogamulizumab-kpkc injection). These patients are not required to "step back" and try a topical corticosteroid and topical imiquimod cream). • With the removal of the above criterion, the criterion for "Initial Therapy" and "Patient is currently receiving Targretin gel or has received Targretin gel in the past" are identical and therefore, the criterion will not distinguish between "Initial Therapy" and "Patient is currently receiving Targretin gel or has received Targretin gel in the past" (i.e., there will be one set of criterion).	
Annual Revision	No criteria changes.	09/30/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Tasigna Prior Authorization Policy
- Tasigna® (nilotinib capsules – Novartis)

REVIEW DATE: 04/01/2020

OVERVIEW

Tasigna, a kinase inhibitor, is indicated for the treatment of adult and pediatric patients ≥1 year of age with newly diagnosed Philadelphia positive (Ph+) chronic myeloid leukemia (CML) in chronic phase (CP).[1] Tasigna is also indicated for the treatment of CP and accelerated phase (AP) Ph+ CML in adult patients resistant or intolerant to prior therapy that included imatinib. Tasigna is also indicated for use in pediatric patients ≥ 1 year of age with Ph+ CML-CP resistant or intolerant to prior TKI therapy.[1] Currently, there are four other tyrosine kinase inhibitors (TKIs) approved for the treatment of Ph+ CML: imatinib, Sprycel® (dasatinib tablets), Bosulif® (bosutinib tablets), and Iclusig® (ponatinib tablets).[2-5] These agents are indicated for the treatment of Ph+ CML in various phases; some TKIs are indicated after resistance or intolerance to prior therapy. Iclusig is approved for patients with T315I-positive CML and in adult patients with CML for whom no other TKI therapy is indicated.[5] Imatinib, Sprycel and Iclusig are also indicated for patients with Ph+ acute lymphoblastic leukemia (ALL).

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for CML (version 3.2020 – January 30, 2020) state that for patients with CP CML with a low-risk score, the primary treatment recommended includes a first-generation TKI (Gleevec or generic imatinib 400 mg QD [Category 1]), or a second-generation TKI (Bosulif 400 mg QD [Category 1], Sprycel 100 mg QD [Category 1], or Tasigna 300 mg BID [Category 1]).[6] For patients with CP CML with an intermediate- or high-risk score, a second-generation TKI is preferred (Bosulif 400 mg QD [Category 1], Sprycel 100 mg QD [Category 1], or Tasigna 300 mg BID [Category 1]). A first-generation TKI (Gleevec or generic imatinib 400 mg QD) is an alternative [Category 2A]. Iclusig is an option for patients with a T315I mutation and for with disease that has not responded to multiple TKIs or in whom another TKI is not indicated.[6]

NCCN guidelines for (ALL [adults and adolescent young adults] {version 1.2020 – January 15, 2020} and Pediatric ALL [pediatric and adolescent young adults] {version 2.2020 – November 25, 2019}recommend Tasigna for patients with in various induction regimens, as well as in relapsed or refractory ALL.[11,12] Tasigna is also recommended for patients with specific mutations and in certain maintenance regimens. Data are also available regarding use of Tasigna in ALL.[13-15]

The NCCN soft tissue sarcoma guidelines (version 6.2019 – February 10, 2020) indicate that Tasigna is a treatment option for patients with gastrointestinal stroma tumor (GIST) who have disease progression after imatinib, Stivarga® (regorafenib tablets), and Sutent® (sunitinib capsules).[7]

Other Uses with Supportive Evidence

Data are available regarding use of Tasigna in GIST. In one Phase III study (n = 248) Tasigna was compared with best supportive care (BSC) [BSC without TKI therapy; BSC plus imatinib; BSC plus Sutent) in patients with GIST resistant to or intolerant of imatinib and Sutent.[8] Median progression-free survival (PFS) was similar between arms (109 days with Tasigna vs. 111 days with BSC; P = 0.56). A trend in longer overall survival (OS) was noted with Tasigna vs. BSC (332 days vs. 280 days; P = 0.29). Tasigna also demonstrated modest activity in one Phase II study (n = 13) in patients with GIST previously treated with imatinib and Sutent.[9] In a randomized, open-label, multicenter, Phase III trial involving patients (aged ≥ 18 years) with histologically-confirmed unresectable or metastatic GIST (n = 647) showed that PFS was higher with imatinib overall compared with Tasigna and that Tasigna is not an ideal first-line treatment for GIST.[10]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Tasigna. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tasigna is recommended in those who meet the following criteria:

FDA-Approved Indications

484. **Chronic Myeloid Leukemia (CML) That is Philadelphia Chromosome Positive (Ph+).** Approve for 3 years.

Other Uses with Supportive Evidence

485. **Acute Lymphoblastic Leukemia (ALL) That is Philadelphia Chromosome Positive (Ph+).** Approve for 3 years if the patient has tried at least one other tyrosine kinase inhibitor that is used for Philadelphia chromosome positive ALL.
Note: Examples include Gleevec® (imatinib tablets) and Sprycel® (dasatinib tablets).

486. **Gastrointestinal Stromal Tumor (GIST).** Approve for 3 years if the patient meets the following criteria (A, B, and C):
F) Patient has tried Gleevec® (imatinib tablets); AND
G) Patient has tried Sutent® (sunitinib capsules); AND
H) Patient has tried Stivarga® (regorafenib tablets).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tasigna is not recommended in the following situations:

253. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

382. Tasigna® capsules [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals, Inc.; September 2019.
383. Gleevec® tablets [prescribing information]. East Hanover, NJ: Novartis; July 2018.
384. Sprycel® tablets [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; December 2018.
385. Bosulif® tablets [prescribing information]. New York, NY: Pfizer Inc; October 2019.
386. Iclusig® tablets [prescribing information]. Cambridge, MA: Takeda/Ariad Pharmaceuticals; January 2020.
387. The NCCN Chronic Myeloid Leukemia Clinical Practice Guidelines in Oncology (Version 3.2020 – January 30, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 17, 2020.
388. The NCCN Soft Tissue Sarcoma Practice Guidelines in Oncology (Version 2.2019 – February 4, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 12. 2019.

389. Reichardt P, Blay JY, Gledерblom H, et al. Phase III study of nilotinib versus best supportive care with or without a TKI in patients with gastrointestinal stromal tumors resistant to or intolerant of imatinib and sunitinib. *Ann Oncol.* 2012;23:1680-1687.
390. Cauchi C, Somaiah N, Engstrom PF, et al. Evaluation of nilotinib in advanced GIST previously treated with imatinib and sunitinib. *Cancer Chemother Pharmacol.* 2012;69:977-982.
391. Blay JY, Shen L, Kang YI, et al. Nilotinib versus imatinib as first-line therapy for patients with unresectable or metastatic gastrointestinal stromal tumours (ENESTg1): a randomized phase 3 trial. *Lancet Oncol*. 2015;16(5):550-560.
392. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (Version 1.2020 – January 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 17, 2020.
393. The NCCN Pediatric Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (Version 2.2020 – November 25, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 30, 2020.
394. Ottmann OG, Larson RA, Kantarjian HM, et al. Phase II study of nilotinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia. *Leukemia*. 2013;27(6):1411-1413.
395. Kantarjian H, Giles F, Wunderle L, et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. *N Engl J Med*. 2006;354:2542-2551.
396. Kim AY, Joo YD, Lim SN, et al, for the Adult Acute Lymphoblastic Leukemia Working Party of the Korean Society of Hematology. Nilotinib combined with multiagent chemotherapy for newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. *Blood*. 2015;126(6):746-756.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	For the indication regarding ALL, changed the criteria from requiring two TKIs to one TKI that is used for Philadelphia chromosome positive ALL. Removed the criteria allowing for approval if the patient has been started on Tasigna for an indication or condition addressed as an approval in the Recommended Authorization section.	03/07/2018
Annual Revision	No criteria changes.	03/20/2019
Annual Revision	The following criteria changes were made: **1. Acute Lymphoblastic Leukemia that is Ph+:** The wording that the patient has tried one other tyrosine kinase inhibitor for acute lymphoblastic leukemia was changed to state "at least one" and examples of tyrosine kinase inhibitors were moved from the criteria to a note.	04/01/2020

ALL – Acute lymphoblastic leukemia; TKI(s) – Tyrosine kinase inhibitor(s).

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Tazverik Prior Authorization Policy

- Tazverik™ (tazemetostat tablets – Epizyme)

REVIEW DATE: 02/03/2021

OVERVIEW

Tazverik, an EZH2 inhibitor, is approved in the following conditions:[1]

- **Epithelioid sarcoma**, in patients ≥ 16 years of age with a metastatic or locally advanced disease not eligible for complete resection.
- **Follicular lymphoma**, in the following situations:
  - In adults with relapsed or refractory disease, whose tumors are positive for an EZH2 mutation as detected by an approved test and who have received at least two prior systemic therapies.
  - In adults with relapsed or refractory disease who have no satisfactory alternative treatment options.

These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Guidelines

Tazverik is addressed in the following guidelines from the National Comprehensive Cancer Network (NCCN):

- **B-cell lymphomas:** Guidelines (version 1.2021 – January 20, 2021) recommend Tazverik be used according to the approved indication.[3] This includes use of Tazverik as a subsequent therapy for follicular lymphoma, in patients with EZH2 mutation positive disease after two prior therapies, or in relapsed or refractory disease with EZH2 wild type or unknown mutation status, in patients who have no satisfactory alternative treatment options.[3]
- **Soft Tissue Sarcoma:** Guidelines (version 1.2021 – October 30, 2020) have been updated to recommend Tazverik as a preferred therapy for treatment of metastatic or locally advanced epithelioid sarcoma not eligible for complete resection.[2] No other therapies are listed for this specific subtype of soft tissue sarcoma. Generally for soft tissue sarcomas, treatment recommendations are based on anatomic site of primary disease (e.g., extremities, trunk, visceral, retroperitoneum, or head and neck).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tazverik. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tazverik is recommended in those who meet the following criteria:

FDA-Approved Indications

141. Epithelioid Sarcoma. Approve for 3 years if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 16 years of age; AND
- **B)** Patient has metastatic or locally advanced disease; AND
- **C)** Patient is not eligible for complete resection.

142. Follicular Lymphoma. Approve for 3 years if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has relapsed or refractory disease; AND
- **C)** Patient meets ONE of the following (i or ii):
  - **i.** Both of the following apply (a and b):
    - **a)** Tumor is positive for an EZH2 mutation; AND
    - **b)** Patient has tried at least two prior systemic therapies; OR
  - **ii.** According to the prescriber, there are no appropriate alternative therapies.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tazverik is not recommended in the following situations:

154. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

487. Tazverik [prescribing information]. Cambridge, MA: Epizyme; June 2020.
488. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (Version 1.2021 – October 30, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 31, 2021.

489. The NCCN B-Cell Lymphoma Clinical Practice Guidelines in Oncology (Version 1.2021 – January 20, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 31, 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/29/2020
Update	02/11/2020: No criteria changes. Updated Overview to include guidelines that address use of Tazverik.	N/A
Selected Revision	**Follicular lymphoma:** This newly approved indication was added to the policy. Criteria align with the FDA-approved use.	06/24/2020
Update	07/10/2020: No criteria changes. Overview was updated to include NCCN recommendations for follicular lymphoma.	N/A
Annual Revision	No criteria changes.	02/03/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Temozolomide Prior Authorization Policy

- Temozolomide capsules (Temodar® – Merck & Co, generic)

REVIEW DATE: 08/12/2020

OVERVIEW

Temozolomide, an alkylating agent, is indicated in adults for the following uses:[1]

- **Anaplastic astrocytoma**, that is refractory, in patients who have experienced disease progression on a drug regimen containing nitrosourea (i.e., BiCNU® [carmustine {BCNU} for injection] or lomustine [CCNU] capsules) and Matulane® (procarbazine capsules).
- **Glioblastoma**, newly diagnosed, concomitantly used with radiotherapy and then as maintenance therapy.

Guidelines

- **Anaplastic Astrocytoma, Glioblastoma, and Other Central Nervous System (CNS) Tumors:** The National Comprehensive Cancer Network (NCCN) CNS cancers clinical practice guidelines (version 2.2020 – April 30, 2020) note temozolomide as a treatment option for the treatment of glioblastoma and anaplastic astrocytoma.[2] Temozolomide is listed for use as monotherapy or as adjuvant therapy (i.e., to be used concurrently with radiation or other chemotherapeutic agents). The guidelines note temozolomide as an option for a myriad of CNS cancers, including anaplastic gliomas (includes mixed anaplastic oligoastrocytoma, anaplastic oligodendroglioma, and other rare anaplastic glioma); intracranial or spinal ependymoma; gliosarcoma; primary CNS lymphoma; low-grade glioma/pilocytic and infiltrative supratentorial astrocytoma/oligodendroglioma; medulloblastoma (as recurrence therapy in patients who have tried other chemotherapeutic agents); and brain metastases from solid tumors (in patients for whom radiation therapy is not an option and who have tried other chemotherapeutic drugs that penetrate the CNS).
- **Ewing's sarcoma or mesenchymal chondrosarcoma:** The NCCN bone cancer guidelines (version 1.2020 – August 12, 2019) note temozolomide as a treatment option in patients with relapsed, refractory, or metastatic disease.[3]
- **Melanoma:** The NCCN cutaneous melanoma guidelines (version 3.2020 – May 18, 2020) note temozolomide as a treatment option in patients with metastatic melanoma.[4]
- **Neuroendocrine tumors**: The NCCN guidelines (version 2.2020 – July 24, 2020) recommends use of temozolomide for neuroendocrine tumors of the gastrointestinal tract, lung or thymus

(carcinoid tumors), pancreas, pheochromocytomas/paragangliomas, and poorly differentiated carcinomas/large or small cell.[5]

- **Mycosis fungoides (MF)/Sezary Syndrome:** The NCCN primary cutaneous lymphomas guidelines (version 2.2020 – April 10, 2020) note temozolomide as a treatment option for this condition in patients who have tried other chemotherapeutic agents; and for primary cutaneous anaplastic large cell lymphoma with multifocal lesions or regional nodes (in patients with CNS involvement).[6,7]
- **Small cell lung cancer:** The NCCN small cell lung cancer guidelines (version 1.2021 – August 4, 2020) note temozolomide as one of the subsequent therapy options for patients with relapsed disease ≤ 6 months.[8] It may be useful in patients with brain metastases.
- **Soft tissue sarcomas:** The NCCN soft tissue sarcoma guidelines (version 2.2020 – May 28, 2020) note temozolomide as a treatment option for angiosarcoma, rhabdomyosarcoma, solitary fibrous tumor; soft tissue sarcomas (in patients with advanced, unresectable, or metastatic disease who have tried other chemotherapeutic agents).[9]
- **Uterine sarcoma:** The NCCN uterine neoplasms guidelines (version 2.2020 – July 24, 2020) note temozolomide as a treatment option for patients with metastatic, recurrent, or medically inoperable uterine sarcoma.[10]
- **Uveal melanoma:** The NCCN uveal melanoma guidelines (version 1.2020 – May 21, 2020) note temozolomide as a treatment option for patients with metastatic or unresectable uveal melanoma.[11]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of temozolomide capsules. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of temozolomide capsules is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Anaplastic Astrocytoma.** Approve for 3 years.

2. **Glioblastoma multiforme (GBM, Glioblastoma, Grade IV Astrocytoma).** Approve for 3 years.

Other Uses with Supportive Evidence

3. **Anaplastic Gliomas (Includes Mixed Anaplastic Oligoastrocytoma, Anaplastic Oligodendroglioma, and Other Rare Anaplastic Gliomas).** Approve for 3 years.

4. **Angiosarcoma.** Approve for 3 years.

5. **Brain Metastases from Solid Tumors.** Approve for 3 years if the patient meets the following criteria (A and B):
   - **A)** Radiation therapy is not an option; AND
   - **B)** At least one chemotherapy drug that penetrates the central nervous system has already been tried.
     Note: Examples of chemotherapy are cyclophosphamide/methotrexate/fluorouracil for breast cancer, carboplatin and etoposide for non-small cell lung cancer.

6. **Ependymoma, Intracranial or Spinal.** Approve for 3 years.

7. **Ewing's Sarcoma or Mesenchymal Chondrosarcoma.** Approve for 3 years in patients with relapsed, refractory or metastatic disease.

8. **Gliosarcoma.** Approve for 3 years.

9. **Low-Grade (WHO Grade I or II) Glioma/ Pilocytic and Infiltrative Supratentorial Astrocytoma/Oligodendroglioma in Adults.** Approve for 3 years.

10. **Medulloblastoma.** Approve for 3 years for recurrence therapy in patients who have received prior chemotherapy.

11. **Melanoma.** Approve for 3 years if the patient has metastatic melanoma.

12. **Mycosis Fungoides/Sézary Syndrome.** Approve for 3 years in patients who have received one prior therapy.

13. **Neuroendocrine Tumors of the Gastrointestinal Tract, Lung or Thymus (Carcinoid Tumors).** Approve for 3 years.

14. **Neuroendocrine Tumors of the Pancreas (Islet Cell Tumors), Pancreatic Neuroendocrine Tumors.** Approve for 3 years.

15. **Neuroendocrine Carcinoma – Poorly Differentiated, Large or Small Cell (Other than Lung), Unknown Primary.** Approve for 3 years.

16. **Pheochromocytoma or Paragangliomas.** Approve for 3 years in patients with metastases.

17. **Primary Central Nervous System Lymphoma.** Approve for 3 years.

18. **Primary Cutaneous Anaplastic Large Cell Lymphoma** Approve for 3 years in patients with relapsed/refractory disease with central nervous system involvement.

19. **Rhabdomyosarcoma.** Approve for 3 years.

20. **Small Cell Lung Cancer.** Approve for 3 years if the patient has tried one chemotherapy regimen.

21. **Soft Tissue Sarcomas.** Approve for 3 years in patients with advanced, unresectable, or metastatic disease.

22. **Solitary Fibrous Tumor.** Approve for 3 years.

23. **Uterine Sarcomas**. Approve for 3 years in patients with metastatic, recurrent or medically inoperable disease.

24. **Uveal Melanoma.** Approve for 3 years for metastatic or unresectable disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of temozolomide capsules is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Temodar® capsules [prescribing information]. White Station, NJ: Merck & Co., Inc (manufactured by Baxter Oncology GmbH, Halle, Germany); September 2015.
2. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (Version 2.2020 – April 30, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 5, 2020.
3. The NCCN Bone Cancer Clinical Practice Guidelines in Oncology (Version 1.2020 – August 12, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 5, 2020.
4. The NCCN Cutaneous Melanoma Clinical Practice Guidelines in Oncology (Version 3.2020 – May 18, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 5, 2020.
5. The NCCN Neuroendocrine and Adrenal Tumors Clinical Practice Guidelines in Oncology (Version 2.2020 – July 24, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 5, 2020.
6. The NCCN Primary Cutaneous Lymphoma Clinical Practice Guidelines in Oncology (Version 2.2020 – April 10, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 5, 2020.
7. The NCCN Drugs & Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 3, 2020. Search terms: temozolomide.
8. The NCCN -Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 1.2021 – August 4, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 10, 2020.
9. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (Version 2.2020 – May 28, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 5, 2020.
10. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (Version 2.2020 – July 24, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 10, 2020.
11. The NCCN Uveal Melanoma Clinical Practice Guidelines in Oncology (Version 1.2020 – May 21, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 10, 2020.

HISTORY

Type of Revision	Summary of Changes*	Review Date
Annual revision	Added new approval conditions for Uveal Melanoma and Neuroendocrine Carcinomas – Poorly Differentiated, Large or Small cell (Other than Lung), Unknown Primary. Deleted the following approval conditions from Other Uses with Supportive Evidence section: Patient has been started on temozolomide and Dermatofibrosarcoma Protuberans (DFSP). Also deleted "Supratentorial Primitive Neuroectodermal Tumor" from Medulloblastoma approval condition.	06/27/2018
Annual revision	Revisions: • **Low-Grade (WHO Grade I or II) Glioma/ Pilocytic and Infiltrative Supratentorial Astrocytoma/Oligodendroglioma in Adults:** The condition of approval was changed to as listed to address pilocytic astrocytoma. Previously, it was listed as Low-Grade Infiltrative Supratentorial Astrocytoma/Oligodendroglioma (excluding pilocytic astrocytoma) in Adults • **Mycosis Fungoides/ Sezary Syndrome:** Criteria were revised to require one prior therapy and examples were removed. Previously, one prior chemotherapy was required and several examples were listed. • **Neuroendocrine Tumors of the Gastrointestinal Tract, Lung or Thymus (Carcinoid Tumors):** This condition of approval was changed to as listed. Previously, it was listed as Neuroendocrine Tumors of the Lung or Thymus (carcinoid tumors). • **Small Cell Lung Cancer:** The list of chemotherapy examples was removed. • **Soft Tissue Sarcomas:** This condition of approval was changed to as listed. Previously, it was listed as Soft Tissue Sarcomas of the Extremities, Superficial Trunk, Head/Neck, or Retroperitoneal/Intra-Abdominal Soft Tissue Sarcomas. The requirement of a trial of one other chemotherapy (single or combination) was removed as it is no longer supported in the National Cancer Center Network (NCCN) guidelines.	07/17/2019

	• **Uterine Sarcomas:** The condition of approval was changed to as listed. Previously, it was listed as Uterine Sarcoma (i.e., High-Grade Endometrial Stromal Sarcoma, Undifferentiated Uterine Sarcoma, Uterine Leiomyosarcoma). • **Primary Cutaneous Large Cell Lymphoma:** The new condition of approval was added. Criteria are to approve for 3 years in patients with relapsed/refractory disease with central nervous system involvement.	
Annual revision	• **Brain Metastases from Solid Tumors**: Instead of "Other chemotherapy drug", rephrased it to say "At least one chemotherapy drug". • **Small Cell Lung Cancer:** Deleted criteria "Patient has metastases to the brain" since it is not part of the guidelines. • **Solitary Fibrous Tumor:** Deleted "Hemangiopericytoma" from indication since it was removed in the guidelines.	08/12/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Tepmetko Prior Authorization Policy
- Tepmetko® (tepotinib tablets – EMD Serono)

REVIEW DATE: 02/08/2021

OVERVIEW
Tepmetko, a kinase inhibitor, is indicated for the treatment of adult patients with **metastatic non-small cell lung cancer (NSCLC)** harboring mesenchymal-epithelial transition **(*MET*) exon 14 skipping alterations**.[1] This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Guidelines
Tepmetko is not addressed in the guidelines. The National Comprehensive Cancer Network (NCCN) non-small cell lung cancer guidelines (version 2.2021 – December 15, 2020) recommend Tabrecta™ (capmatinib tablets) as the "preferred" first-line therapy (category 2A) in patients with *MET* exon 14 skipping mutation discovered prior to first-line systemic therapy. Xalkori® (crizotinib capsules) is recommended (category 2A) as "useful in certain circumstances" in this setting. In patients with *MET* exon 14 skipping mutation discovered during first-line systemic therapy, Tabrecta or Xalkori are recommended (both category 2A) after completion of planned systemic therapy or systemic therapy can be interrupted followed by either one of these targeted therapies.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Tepmetko. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Tepmetko is recommended in those who meet the following criteria:

FDA-Approved Indications

490. **Non-Small Cell Lung Cancer (NSCLC).** Approve for 3 years if the patient meets the following criteria (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has metastatic disease; AND
   C) The tumor is positive for mesenchymal-epithelial transition (*MET*) exon 14 skipping alterations.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Tepmetko is not recommended in the following situations:

8. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

20. Tepmetko® tablets [prescribing information]. Rockland, MA: EMD Serono, Inc.; February 2021.
21. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 2.2021 – December 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 3, 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	02/08/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Thalomid Prior Authorization Policy
- Thalomid® (thalidomide capsules – Celgene)

REVIEW DATE: 04/01/2020

OVERVIEW
Thalomid is indicated for use in combination with dexamethasone for the treatment of patients with newly diagnosed multiple myeloma.[1] It is also indicated for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL). It is not indicated as monotherapy for such ENL treatment in the presence of moderate to severe neuritis. Thalomid is also indicated as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence.

Guidelines
The National Comprehensive Cancer Network (NCCN) guidelines for multiple myeloma (version 3.2020 – March 10, 2020) recommend use of Thalomid in various scenarios.[2] It is considered useful in certain circumstances among patients with previously treated multiple myeloma, as well as for primary therapy for transplant candidates.

The National Comprehensive Cancer Network (NCCN) has guidelines regarding myeloproliferative neoplasms (version 3.2019 – September 4, 2019) that discuss myelofibrosis.[3] Thalomid is recommended in the management of anemia associated with myelofibrosis, with or without prednisone, for patients with erythropoietin levels ≥ 500 mU/mL.

The NCCN guidelines for acquired immune deficiency syndrome (AIDS)-Related Kaposi Sarcoma (version 1.2020 – February 12, 2020) recommended Thalomid as an agent useful under certain conditions for

subsequent systemic therapy options for relapsed/refractory therapy.[4] First-line systemic therapy options include liposomal doxorubicin (preferred), and paclitaxel. Other subsequent systemic therapy options for relapsed/refractory therapy are also cited (e.g., Pomalyst® [pomalidomide capsules] {preferred}, Revlimid® [lenalidomide], imatinib).

The National Comprehensive Cancer Network (NCCN) guidelines for B-Cell Lymphomas (version 1.2020 – January 22, 2020) recommend use of Thalomid, with or without rituximab, for patients with Castleman's disease who have relapsed/refractory or progressive disease.[5] Thalomid is cited as an other recommended therapy (when given with cyclophosphamide and prednisone) for hyaline vascular histology for patients with multicentric Castleman's disease who are negative for the human immunodeficiency virus (HIV) and human herpesvirus-8 (HHV-8).

Other Uses with Supportive Evidence

Some data support the use of Thalomid for ENL, although the condition is not common and data are limited.[6,7] Data indicates that Thalomid does successfully and quickly improve the cutaneous manifestations of ENL and in some patients the steroid requirement was reduced.

Thalomid has been used for discoid lupus erythematosus and cutaneous lupus erythematosus. Patients usually had refractory disease after trial of other therapies and good responses were achieved for many patients given Thalomid.[8-17] A retrospective medical review was done and involved 29 patients with refractory cutaneous manifestations of cutaneous lupus erythematosus who received Thalomid. Of the 23 patients who took Thalomid for 1 month, 74% of patients (n = 17/23) had complete resolution of the cutaneous manifestations and 13% of patients (n = 3/23) had a 75% or greater partial improvement.[11] Another report involving patients with discoid lupus (n = 18), subacute cutaneous lupus (n = 6), and systemic lupus erythematosus with skin involvement (n = 24) who had been resistant to at least two other treatments found a response rate of 81% (n = 39/48) with use of Thalomid with 60% of patients (n = 29/48) achieving a complete cutaneous remission.[12] Other therapies used for these conditions include antimalarial agents (e.g. hydroxychloroquine), corticosteroids (oral, topical, intralesional), methotrexate, azathioprine, cyclosporine, dapsone, mycophenolate mofetil, topical calcineurin inhibitors (e.g., Elidel, Protopic) and Soriatane.[10,15]

Thalomid has been studied in patients with prurigo nodularis, most of whom were refractory to other treatments or with adverse events (AEs) from the other therapies.[8,18,19] A retrospective review assessed the medical records of 42 patients with prurigo nodularis who were refractory to other therapy and who received Thalomid.[18] Patients received Thalomid for an average of 105 weeks. Previous therapies tried included topical steroids, intralesional steroids, systemic steroids, topical tar, macrolides, cyclosporine, azathioprine, methotrexate, calcineurnin inhibitors, antihistamines, dapsone, capsaicin, laser therapy, PUVA, UVB, retinoids, hydroxyzine, and macrolides. With Thalomid, improvement was noted in approximately one-third of patients.

Recurrent aphthous ulcers and recurrent aphthous stomatitis are associated with frequent and recurring symptoms that are painful and can lead to difficulty in speaking, eating, and swallowing.[20-23] Ulcers are larger and may persist for weeks to months. The conditions are noted in certain disease states such as in patients who are human immunodeficiency virus (HIV)-positive and Bechet's disease. In general, few adequately powered trials have assessed the efficacy of therapeutic agents for aphthous ulcers or aphthous stomatitis.[20] Although the data are older and limited, Thalomid has led to rapid resolution of symptoms in patients with recurrent aphthous ulcers or aphthous stomatitis.[24-29] A double-blind, randomized, placebo-controlled study assessed Thalomid as a therapy for oral aphthous ulcers in patients infected with HIV. In total, 55% of patients (n = 16/29) given Thalomid had complete healing of their aphthous ulcers after 4 weeks compared with only 7% of patients (n = 2/28) who received placebo. Patients given Thalomid had symptom improvements in regards to discomfort that occurred while eating.[25] A retrospective cohort study

involving patients with recurrent aphthous stomatitis found that Thalomid was rapidly effective as 85% of patients (n = 78/92) achieved a complete remission of the condition within 14 days.[29] Many other agents have been used for recurrent aphthous ulcers or stomatitis including topical or intralesional corticosteroids, systemic corticosteroids, topical anesthetics/analgesics (lidocaine 2% viscous solution, benzocaine lozenges), antimicrobial mouth washes (tetracycline, chlorhexidine), topical sucralfate, acyclovir, pentoxifylline, dapsone, colchicine, and azathioprine.[20-23] Due to toxicities, use of Thalomid is generally reserved for patients who have not obtained satisfactory results with other agents.[30,31]

Safety

Thalomid has a Boxed Warning regarding embryofetal toxicity and venous thromboembolism. The safety and effectiveness in pediatric patients < 12 years of age have not been established. Thalomid is available only through the THALOMID Risk Evaluation Mitigation Strategy (REMS™) program. Males and females must follow the required reproductive precautions.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Thalomid. All approvals are provided for 3 years in duration.

Automation: None.

Recommended Authorization Criteria

Coverage of Thalomid is recommended in those who meet the following criteria:

FDA-Approved Indications

2. **Erythema Nodosum Leprosum (ENL).** Approve for 3 years.

3. **Multiple Myeloma.** Approve for 3 years.

Other Uses with Supportive Evidence

3. **Acquired Immune Deficiency Syndrome (AIDS)-Related Kaposi's Sarcoma.** Approve for 3 years if the patient meets the following (A and B):
   - **A)** The patient has tried at least one regimen or therapy; AND
     Note: Examples include liposomal doxorubicin, paclitaxel, Pomalyst® (pomalidomide capsules), Revlimid® [lenalidomide], and imatinib.
   - **B)** The patient has relapsed or refractory disease.

4. **Castleman's Disease.** Approve for 3 years if the patient meets one of the following (A or B):
   - **A)** The patient has relapsed/refractory or progressive disease; OR
   - **B)** The patient meets all of the following (i, ii, and iii):
     - **i.** The patient has multicentric Castleman's disease; AND
     - **ii.** The patient is negative for the human immunodeficiency virus (HIV) and human herpesvirus-8 (HHV-8); AND
     - **iii.** The patient has hyaline vascular histology.

5. **Discoid Lupus Erythematosus or Cutaneous Lupus Erythematosus.** Approve for 3 years if the patient has tried at least two other therapies.

Note: Examples of therapies include corticosteroids (oral, topical, intralesional), antimalarial agents (e.g., hydroxychloroquine), topical calcineurin inhibitors (e.g., Protopic® [tacrolimus ointment], Elidel® [pimecrolimus cream]), azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, dapsone, and Soriatane® (acitretin capsules).

6. **Myelofibrosis.** Approve for 3 years if the patient meets the following criteria (A and B):
   A) According to the prescriber the patient has anemia; AND
   B) The patient has serum erythropoietin levels ≥ 500 mU/mL.

7. **Prurigo Nodularis.** Approve for 3 years if the patient has tried at least two other therapies.
   Note: Examples of therapies include topical steroids, intralesional steroids, systemic steroids, topical tar, cyclosporine, macrolides, azathioprine, methotrexate, topical calcineurin inhibitors (Elidel, Protopic), retinoids, antihistamines, hydroxyzine, dapsone, capsaicin, psoralen plus ultraviolet A (PUVA) therapy, and ultraviolet B (UVB) therapy.

8. **Recurrent Aphthous Ulcers or Aphthous Stomatitis.** Approve for 3 years if the patient has tried at least two other therapies.
   Note: Examples include topical or intralesional corticosteroids, systemic corticosteroids, topical anesthetics/analgesics (e.g., lidocaine 2% viscous solution, benzocaine lozenges), antimicrobial mouthwashes (e.g., tetracycline, chlorhexidine), topical sucralfate, acyclovir, pentoxifylline, dapsone, colchicine, and azathioprine.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Thalomid has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

254. Cancer Cachexia. Several small studies are available that have investigated Thalomid in the management of cancer cachexia related to various cancers.[32-36] A single center double-blind, controlled trial randomized patients with pancreatic cancer who had lost at least 10% of their body weight to receive Thalomid or placebo for 24 weeks (n = 50).[33] Of the 33 patients evaluable at 4 weeks, patients given Thalomid had gained an average of 0.37 kg compared with a loss of 2.21 kg in the patients given placebo.[33] A published review of data regarding use of Thalomid for the management of cancer cachexia concluded that there is inadequate evidence to recommend Thalomid in clinical practice.[36]

255. Crohn's Disease. Several publications report use of Thalomid in patients with Crohn's disease.[37-53] Thalomid was used as an adjunctive therapy, or in those refractory to other therapy, and usually involved children. The data were not of high quality and primarily consisted of open-label designs or retrospective reviews, without a placebo control, and involved very few patients.[37-53] Guidelines from the American College of Gastroenterology (2018) for the management of Crohn's disease in adults do not mention Thalomid as a therapeutic alternative.[48] Although some improvements were noted in published data with Thalomid, more definite data from randomized, controlled trials are required before this is a recommended therapy.[48] Consensus guidelines of the European Crohn's and Colitis Organization (ECCO) and the European society of Pediatric Gastroenterology, Hepatology and Nutrition (ESOGGAN) [2014] state that even though some data are available that suggest efficacy of Thalomid in refractory pediatric Crohn's disease, there are insufficient data to recommended Thalomid therapy at this juncture.[53] Many other therapies are available for the management of Crohn's disease.

256. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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6. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (Version 3.2020 – March 10, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 13, 2020.
7. The NCCN Myeloproliferative Neoplasms Clinical Practice Guidelines in Oncology (Version 3.2019 – September 4, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 13, 2020.
8. The NCCN AIDS-Related Kaposi Sarcoma Clinical Practice Guidelines in Oncology (Version 1.2020 – February 12, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 13, 2020.
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HISTORY

Type of Revision	Summary of Changes*	Review Date
Annual Revision	No criteria changes.	03/07/2018
Annual Revision	Added approval for patients with acquired immune deficiency syndrome (AIDS)-Related Kaposi's Sarcoma for 3 years if the patient has tried one regimen therapy (e.g., liposomal doxorubicin, paclitaxel, Pomalyst® [pomalidomide capsules], imatinib) and the patient has relapsed or refractory disease. Added criteria to approve for Castleman's disease in patients with relapsed/refractory or progressive disease.	03/20/2019
Annual Revision	The following changes were made: **1. Acquired Immune Deficiency Syndrome-Related Kaposi's Sarcoma:** The requirement that the patient has tried one regimen or therapy was changed to state "at least" and the examples of agents were moved to a note, with Revlimid added. **2. Castleman's Disease:** Criteria were added to approve for 3 years if the patient has multicentric Castleman's disease, is negative for the human immunodeficiency virus and human herpesvirus-8, and has hyaline vascular histology. The previous criteria that allowed approvals if the patients had relapsed/refractory or progressive disease remains.	04/01/2020

	3. **Discoid Lupus Erythematosus or Cutaneous Lupus Erythematosus:** The requirement that the patient has two other therapies was changed to state "at least" and the examples of agents were moved to a note. 4. **Myelofibrosis:** Criteria were revised to include that according to the prescriber the patient has anemia and that serum erythopoetin levels are ≥ 500 mU/mL. With the addition of this criteria, the requirement that the patient has tried one other therapy was removed. 5. **Prurigo Nodularis:** The requirement that the patient has two other therapies was changed to state "at least" and the examples of agents were moved to a note. 6. **Recurrent Aphthous Ulcers or Aphthous Stomatitis:** The requirement that the patient has two other therapies was changed to state "at least" and the examples of agents were moved to a note. 7. **Systemic Light Chain Amyloidosis:** The criteria to approve for this condition was removed. It is not recommended in NCCN guidelines. 8. **Waldenstrom's Macroglobulinemia/Lymphoplastmacytic Lymphoma:** The criteria to approve for this condition was removed. It is not recommended in NCCN guidelines. 9. **Conditions Not Recommended for Approval:** The following indications were removed from the policy: breast cancer; glioblastoma multiforme; hepatocellular carcinoma; metastatic renal cell carcinoma; and myelodysplastic syndromes. NCCN guidelines do not recommend use of these therapies and there is a lack of recent literature recommending use of these agents.	

AIDS – Acquired immune deficiency syndrome; NCCN – National Comprehensive Cancer Network.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Tibsovo Prior Authorization Policy
- Tibsovo® (ivosidenib tablets – Agios)

REVIEW DATE: 02/10/2021

OVERVIEW

Tibsovo, an isocitrate dehydrogenase-1 (IDH1) inhibitor, is indicated for the following uses in patients with a susceptible IDH1 mutation as detected by an FDA-approved test:[1]

- **Acute myeloid leukemia (AML), treatment in adults with newly diagnosed disease** who are ≥ 75 years of age who have comorbidities that preclude use of intensive induction chemotherapy.
- **Acute myeloid leukemia in adults with relapsed or refractory disease**.

Data are available regarding use of Tibsovo in patients with IDH1-mutatant chemotherapy-refractory cholangiosarcinoma[2] and chondrosarcoma[3].

Disease Overview

AML is a heterogeneous hematologic malignancy hallmarked by clonal expansion of myeloid blasts in the peripheral blood, bone marrow, and/or other tissues.[4] Undifferentiated blast cells proliferate in bone marrow instead of maturing into normal blood cells. Among adults, it is the most common form of acute leukemia and accounts for the largest number of annual deaths from leukemias in the US. An estimated 21,450 individuals will be diagnosed with AML in 2019 and 10,920 are projected to die from the condition. The median age at diagnosis is 67 years. Diagnosis occurs at ≥ 65 years of age for 54% of patients with around one-third of patients diagnosed at ≥ 75 years of age. The incidence of AML increases as the population ages. Environmental factors such as prolonged exposure to petrochemicals, solvents such as benzene, pesticides, and ionizing radiation have been established to increase the risks for AML, as well as myelodysplastic syndrome (MDS).[4] The cure rates of AML have improved with this outcome noted in 35% to 40% of adult patients who are ≤ 60 years of age and 5% to 15% for patients who are > 60 years of age.[5] However, among patients who are older and unable to receive intensive chemotherapy the survival

rates are dismal with a median survival of only 5 to 10 months.[5] Various gene mutations are present in adults with AML.[4,5] The incidence of IDH1 mutations have been reported in 6% to 9% of AML cases.[6]

Guidelines

Various guidelines by the National Comprehensive Cancer Network (NCCN) address Tibsovo.[2]

- **Acute Myeloid Leukemia:** NCCN guidelines for AML (version 2.2021 – November 12, 2020) cite Tibsovo as a preferred therapy for treatment induction for patients with the IDH1 mutation, as well as in the setting of relapsed or refractory disease (category 2A).[4]
- **Cholangiosarcinoma:** NCCN guidelines for hepatobiliary cancers (version 5.2020 – August 4, 2020) cite Tibsovo useful in certain circumstances for patients with cholangiocarcinoma with IDH1 mutations.[7]
- **Chondrosarcoma:** The NCCN guidelines for bone cancer (version 1.2021 – November 20, 2020) cite Tibsovo for conventional (grades 1 to 3) and dedifferentiated chondrosarcoma in patients with susceptible IDH1 mutations.[8]

Safety

Tibsovo has a Boxed Warning regarding differentiation syndrome.[1] Warnings and Precautions include QTc interval prolongation and Guillain-Barre Syndrome.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tibsovo. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tibsovo is recommended in those who meet the following criteria:

FDA-Approved Indication

~~53.~~50. **Acute Myeloid Leukemia (AML).** Approve for 3 years if the patient meets the following criteria (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Disease is isocitrate dehydrogenase-1 (IDH1) mutation positive as detected by an approved test.

Other Uses with Supportive Evidence

~~54.~~51. **Cholangiocarcinoma.** Approve for 3 years if the patient meets both of the following (A, B and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Disease is isocitrate dehydrogenase-1 (IDH1) mutation positive; AND
- **C)** Patient has been previously treated with at least one chemotherapy regimen.
  Note: Examples are gemcitabine plus cisplatin; 5-fluorouracil plus oxaliplatin or cisplatin; capecitabine + oxaliplatin or cisplatin; gemcitabine + Abraxane® (paclitaxel protein-bound particles for injectable suspension) or capecitabine or oxaliplatin; and FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin).

~~55.~~52. **Chondrosarcoma.** Approve for 3 years if the disease is isocitrate dehydrogenase-1 (IDH1) mutation positive.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tibsovo is not recommended in the following situations:

257. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

270. Tibsovo® tablets [prescribing information]. Cambridge, MA: Agios; May 2019.
271. Abou-Alfa GK, Macarulla T, Javle MM, et al. Ivosidenib in IDH1-mutation chemotherapy-refractory cholaniocarcinoma (CLARIDHy): a multicenter, randomized, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol*. 2020;21(6):796-807.
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276. The NCCN Hepatobiliary Cancers Clinical Practice Guidelines in Oncology (version 5.2020 – August 4, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 1, 2021.
277. The NCCN Bone Cancers Clinical Practice Guidelines in Oncology (version 1.2021 – November 20, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 1, 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	Added criteria to approve if the patient is IDH1 mutation-positive "as deleted by an approved test".	02/06/2019
Annual Revision	No criteria changes.	02/05/2020
Annual Revision	The following changes were made: 1. **Acute Myeloid Leukemia:** Added criteria that the patient is ≥ 18 years of age. 2. **Cholangiocarcinoma:** Criteria were added to approve for 3 years if the patient is ≥ 18 years of age, the disease is IDH1 mutation positive, and the patient has been previously treated with at least one chemotherapy regimen. Examples of chemotherapy regimens are provided in a Note. 3. **Chondrosarcoma:** Criteria were added to approve for 3 years if the disease is IDH1 mutation positive.	02/10/2021

IDH1 – Isocitrate dehydrogenase-1.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Tukysa™ (tucatinib tablets – Seattle Genetics, Inc.)

DATE REVIEWED: 04/22/2020

OVERVIEW

Tukysa is indicated in combination with trastuzumab and capecitabine for the treatment of adult patients with advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.[1]

Guidelines

Tukysa is not addressed in the guidelines. According to the National Comprehensive Cancer Network (NCCN) breast cancer guidelines (version 3.2020 – March 6, 2020), Enhertu is a recommended therapy, as per its FDA-approved indication after two or more prior HER2-targeted therapies, for the treatment of recurrent or Stage IV metastatic disease that is HER2-positive.[2] Trastuzumab + Perjeta + docetaxel is category 1, preferred regimen; or trastuzumab + Perjeta + paclitaxel (category 2A, preferred). Other recommended regimens include: Kadcyla; trastuzumab + vinorelbine, trastuzumab + capecitabine, Tykerb (lapatinib tablets) + capecitabine, and trastuzumab + Tykerb. For HR+, HER2-positive disease, endocrine therapy options include aromatase inhibitor ± trastuzumab; aromatase inhibitor + trastuzumab ± Tykerb; fulvestrant ± trastuzamab, tamoxifen ± trastuzumab (all category 2A). For premenopausal patients, ovarian ablation or suppression is recommended in addition to endocrine therapy ± trastuzumab.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Tukysa. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tukysa is recommended in those who meet the following criteria:

FDA-Approved Indications

491. **Breast Cancer.** Approve for 3 years if the patient meets ALL of the criteria (A, B, and C):
   - **A)** The patient has advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive disease; AND
   - **B)** The patient has received at least one prior anti-HER2-based regimen in the metastatic setting.
     Note: Examples of anti-HER2-based regimens include Perjeta (pertuzumab injection for intravenous use) + trastuzumab + docetaxel, Perjeta + trastuzumab + paclitaxel; Kadcyla (ado-trastuzumab emtansine for intravenous use), trastuzumab + capecitabine, trastuzumab + Tykerb (lapatinib tablets); AND
   - **C)** The medication is used in combination with trastuzumab and capecitabine.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Tukysa has not been shown to be effective or there are limited or preliminary data that are not supportive of general approval for the following conditions.

9. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

22. Tukysa™ tablets [prescribing information]. Bothell, WA: Seattle Genetics, Inc.; April 2020.
23. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 3.2020 – March 6, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on April 19, 2020.

HISTORY

Type of Revision	Summary of Changes*	Date Reviewed
New policy	New criteria	04/22/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Turalio Prior Authorization Policy
- Turalio® (pexidartinib capsules – Daiichi Sankyo)

REVIEW DATE: 07/29/2020

OVERVIEW

Turalio, a kinase inhibitor, is indicated for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery.[1] Turalio targets the colony stimulating factor 1 (CSF1) receptor ; it also inhibits KIT proto-oncogene receptor tyrosine kinase ,as well as FMS-like tyrosine kinase 3 with an internal tandem duplication mutation. Due to the risk of hepatotoxicity, Turalio is only available through a restricted Risk Evaluation and Mitigation Strategy (REMS) program.

Disease Overview

TGCTs are rare, benign tumors of the synovium (joint lining), bursae, and tendon sheath.[2] Tumors cause thickening and overgrowth of the affected tissues, leading to pain, swelling, and reduced mobility. Disease is caused by a chromosomal translocation resulting in CSF1 overexpression, leading to macrophage recruitment and inflammation. The exact incidence is unknown but is estimated at approximately 43 cases per 1 million in the general population, of which approximately 10% are the diffuse subtype (also known as pigmented villonodular synovitis).[2,3] Diffuse TGCTs have a high recurrence rate after surgery of up to 50%, often with multiple recurrences.[4] Untreated or recurrent disease can lead to damage and degeneration of the affected joint. Disease typically affects a single joint, most commonly the knee or hip.

Guidelines

According to the National Comprehensive Cancer Network (NCCN) guidelines for soft tissue sarcoma (version 2.2020 – May 28, 2020), Turalio (category 1) and imatinib (category 2A) are preferred regimens for systemic therapy in TGCT.[5]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Turalio. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Turalio is recommended in those who meet the following criteria:

FDA-Approved Indications

1) **Tenosynovial Giant Cell Tumor (Pigmented Villonodular Synovitis).** Approve for 3 years if, according to the prescriber, the tumor is not amenable to improvement with surgery.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Turalio is not recommended in the following situations:

258. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

278. Turalio® [prescribing information]. Basking Ridge, NJ: Daiichi Sankyo; April 2020.
279. Tenosynovial giant cell tumor. National Organization for Rare Disorders. Updated 2017. Available at: https://rarediseases.org/rare-diseases/tenosynovial-giant-cell-tumor/. Accessed on July 21, 2020.
280. Tap WD, Gelderblom H, Palmerini E, et al. Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial. *Lancet*. 2019;394(10197):478-487.
281. Lucas DR. Tenosynovial giant cell tumor: case report and review. *Arch Pathol Lab Med.* 2012;136(8):901-906.
282. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (Version 2.2020 – May 28, 2020). © 2020 National Comprehensive Cancer Network Inc. Available at: http://www.nccn.org. Accessed July 21, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/05/2019
Annual Revision	No changes to criteria.	07/29/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Ukoniq Prior Authorization Policy
- Ukoniq™ (umbralisib tablets – TG Therapeutics)

REVIEW DATE: 02/10/2021

OVERVIEW
Ukoniq, a phosphoinositide 3-kinase delta (PI3Kδ) and casein kinase (CK1ε) inhibitor, is indicated for the following uses:[1]
- **Follicular lymphoma**, in adults with relapsed or refractory disease who have received at least three prior lines of systemic therapy.
- **Marginal zone lymphoma**, in adults with relapsed or refractory disease who have received at least one prior anti-CD20-based regimen.

Both indications have been approved under accelerated approval based on overall response rate. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Guidelines
Ukoniq is not addressed in the National Comprehensive Cancer Network treatment guidelines.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Ukoniq. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Ukoniq is recommended in those who meet the following criteria:

FDA-Approved Indications

143. Follicular Lymphoma. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has received at least three prior lines of systemic therapy.
  Note: Examples of systemic therapy include bendamustine + rituximab, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CVP (cyclophosphamide, vincristine, prednisone), and Revlimid® (lenalidomide capsule) + rituximab.

144. Marginal Zone Lymphoma. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has received at least one prior anti-CD20-based regimen.
  Note: Examples of anti-CD20-based therapy includes rituximab, rituximab + Revlimid® (lenalidomide capsule), and Gazyva® (obinutuzumab injection for intravenous use) + bendamustine.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ukoniq is not recommended in the following situations:

155. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

492. Ukoniq™ tablets [prescribing information]. Edison, NJ: TG Therapeutics; February 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	02/10/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Valchlor Prior Authorization Policy

- Valchlor® (mechlorethamine gel for topical use – Helsinn Therapeutics)

REVIEW DATE: 10/28/2020

OVERVIEW

Valchlor, a nitrogen mustard, is indicated for the topical treatment of stage IA and IB **mycosis fungoides-type cutaneous T-cell lymphoma** in patients who have received prior skin-directed therapy.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for **primary cutaneous lymphomas** (version 1.2021 – October 12, 2020) recommend Valchlor for the topical treatment of primary cutaneous B-cell lymphoma, mycosis fungoides/Sezary syndrome, and primary cutaneous CD30+ T-cell lymphoproliferative disorders.[2,3]

The NCCN guidelines for **T-cell lymphomas** (version 1.2021 – October 5, 2020) recommends Valchlor for the topical treatment of adult T-cell leukemia/lymphoma – chronic/smoldering subtype.[2,4]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Valchlor. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Valchlor is recommended in those who meet the following criteria:

FDA-Approved Indications

145. Cutaneous Lymphomas Note: Includes mycosis fungoides/Sezary syndrome, primary cutaneous B-cell lymphoma, primary cutaneous CD30+ T-cell lymphoproliferative disorders. Approve for 3 years.

Other Uses with Supportive Evidence

146. Adult T-Cell Leukemia/Lymphoma. Approve for 3 years if the patient has chronic/smoldering subtype of adult T-cell leukemia/lymphoma.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Valchlor is not recommended in the following situations:

156. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

493. Valchlor® gel [prescribing information]. Iselin, NJ: Helsinn Therapeutics; January 2020.
494. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 14, 2020. Search term: mechlorethamine.
495. The NCCN Primary Cutaneous Lymphomas Clinical Practice Guidelines in Oncology (Version 1.2021 – October 12, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 14, 2020.
496. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 1.2021 – October 5, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 14, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/16/2019
Annual Revision	No criteria changes.	10/28/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Venclexta Prior Authorization Policy

- Venclexta® (venetoclax talets – AbbVie and Genentech)

REVIEW DATE: 06/03/2020

OVERVIEW

Venclexta, a B-cell lymphoma-2 (BCL-2) inhibitor, is indicated for the treatment of adults with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).[1] Additionally, Venclexta is indicated for use in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly diagnosed acute myeloid leukemia (AML) in adults who are ≥ 75 years of age or who have comorbidities that preclude use of intensive induction chemotherapy.

Disease Overview

CLL is one of the most prevalent adult leukemias in the Western world.[2] In 2019, an estimated 20,720 patients will be diagnosed with CLL in the US, and approximately 3,930 patients will die from the disease. The condition usually is diagnosed in older adults (≥ 70 years of age) and occurs more frequently in men. The leukemic cells appear as small, mature lymphocytes. CLL and SLL are different manifestations of the same condition and are managed similarly. In CLL, many of the abnormal lymphocytes are found in the blood, as well as in the bone marrow and lymphoid tissue. In SLL, there are few, if any, abnormal lymphocytes circulating in blood and most of the disease is in the lymph nodes, bone marrow, and other lymphoid tissue. The diagnosis requires the presence of at least 5 x 10^9/L monoclonal B-lymphocytes in the peripheral blood. SLL requires the presence of lymphadenopathy and/or splenomegaly with < 5 x 10^9/L B-lymphocytes found in the peripheral blood.

AML is a heterogeneous hematologic malignancy that is hallmarked by clonal expansion of myeloid blasts in the peripheral blood, bone marrow, and/or other tissues.[3] It is a rather common form of acute leukemia in adults and it has the largest number of annual deaths from leukemias in the US. Around 21,450 people will be diagnosed with AML in 2019, and 10,920 patients will die from the condition. The median age at diagnosis is 67 years. Over one-half and approximately one-third of patients receive the diagnosis at ≥ 65 and ≥ 75 years of age, respectively. The incidence of AML, along with myelodysplastic syndrome (MDS) is rising as patients become older. Environmental factors play a role and include prolonged exposure to petrochemicals; solvents such as benzene; pesticides; and ionizing radiation. Also, two cytotoxic agents that are associated with therapy-related MDS/AML are alkylating agents (e.g., cyclophosphamide) and topoisomerase inhibitors (e.g., doxorubicin). Antimetabolite therapy, notably fludarabine, has also been associated with MDS/AML in patients with lymphoproliferative disorders, especially when given in combination with alkylating agents. Molecular or karyotypic abnormalities can also be identified. Treatment of AML can involve the following modalities at various stages: chemotherapy, radiation therapy, chemotherapy with stem cell transplant, and other drug therapy.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for CLL/SLL (version 4.2020 – December 20, 2019) cite Venclexta in several scenarios.[2] Venclexta plus Gazyva® (obinutuzumab injection for intravenous use) is listed as a first-line therapy (preferred regimen) in frail patients with comorbidities, patients ≥ 65 years, and in younger patients with significant comorbidities without 17p deletion/TP53 mutation (category 2A). This regimen is also cited as another recommended regimen (category 2B) in patients < 65 years of age without significant comorbidity. Venclexta plus rituximab is listed as preferred regimen option for patients with relapsed/refractory therapy without 17p deletion (category 1).[3] The NCCN also cite Venclexta as an option for relapsed/refractory therapy among patients with CLL without deletion 17p/TP53 mutation (category 2A).[3] For patients with 17p deletion/TP53 mutation, Venclexta plus Gazyva is recommended as a preferred regimen first-line (category 2A). Also, among this population, Venclexta with rituximab (category 1) and Venclexta alone (category 2A) are recommended in patients with relapsed or refractory disease as preferred regimens. Many other first-line options are recommended. CLL and SLL are different manifestations of the same diseases which are managed similarly.[3]

NCCN guidelines for AML (version 3.2020 – December 23, 2019) recommend Venclexta (in combination with decitabine, azacitidine or low-dose cytarabine) for treatment induction in patients ≥ 60 years of age who are candidates for intensive remission induction therapy with unfavorable-risk cytogenetics.[3] It is also recommended in other induction therapy clinical scenarios in patients who are not candidates for intensive remission. Venclexta (along with decitabine, azacitidine, or low-dose cytarabine) is also recommended as AML post-induction therapy for patients ≥ 60 years of age.

The NCCN guidelines for B-Cell Lymphomas (version 1.2020 – January 22, 2020) address mantle cell lymphoma. Venclexta is cited as a preferred second-line therapy regimen (category 2A) in patients with a short response duration to prior chemoimmunotherapy.[4] Other regimens recommended second-line are Venclexta plus Imbruvica (category 2B). Venclexta is recommended as an other recommended regimen in patients with an extended response duration to prior chemoimmunotherapy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Venclexta. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Venclexta is recommended in those who meet the following criteria:

FDA-Approved Indications

~~56.~~53. **Chronic Lymphocytic Leukemia (CLL).** Approve for 3 years.

~~57.~~54. **Small Lymphocytic Lymphoma (SLL).** Approve for 3 years.

~~58.~~55. **Acute Myeloid Leukemia (AML).** Approve for 3 years if the patient is using Venclexta in combination with either azacitidine, decitabine, or cytarabine.

Other Uses with Supportive Evidence

~~59.~~56. **Mantle Cell Lymphoma.** Approve for 3 years if the patient has tried at least one prior therapy. Note: Examples of therapies include Imbruvica® (ibrutinib capsules and tablets) with or without rituximab; Calquence® (acalabrutinib capsules); Revlimid® (lenalidomide capsules) with or without rituximab; RDHAP (rituximab, dexamethasone, cytarabine, cisplatin); alternating RCHOP/RDHAP [rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone/rituximab, dexamethasone, cytarabine, cisplatin]; HyperCVAD (cyclophosphamide vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) plus rituximab; RCHOP; or Treanda® (bendamustine injection for intravenous use) plus rituximab.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Venclexta is not recommended in the following situations:

259. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

397. Venclexta® tablets [prescribing information]. North Chicago, IL and South San Francisco, CA: AbbVie and Genentech (a member of the Roche Group); July 2019.
398. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (Version 4.2020 – December 20, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at http://www.nccn.org. Accessed on May 28, 2020.
399. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (Version 3.2020 – December 23, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 28, 2020.
400. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 1.2020 – January 22, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at http://www.nccn.org. Accessed on May 28, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Added criteria for mantle cell lymphoma and small lymphocytic lymphoma per NCCN guidelines. The alternatives were changed for patients with CLL and CLL with 17p deletion in-line with NCCN guidelines.	05/16/2018
Selected Revision	Criteria were updated to reflect that Venclexta is now FDA-approved for CLL with or without the 17p deletion. Prior to this, the product was FDA-approved only for 17p deletion CLL; however, the criteria previously addressed both settings. The specific approval condition and related criteria for CLL with 17p deletion were deleted. The criteria for CLL was moved from the Other Uses with Supportive Evidence Section to	06/20/2018

	the FDA-Approved Indications section. The alternatives cited that qualify as a trial of one prior therapy for CLL, which is required before approval, were merged such that no changes were needed in the listing of agents. Criteria were updated to reflect that Venclexta is now indicated for SLL, with or without 17p deletion. The criteria addressing SLL, which require that the patient has tried one prior therapy, was moved from the Other Uses with Supportive Evidence Section to the FDA-approved indications section.	
Selected Revision	Criteria added to address the new indication for AML.	11/28/2018
Selected Revision	Criteria regarding the diagnosis of AML were revised per guidance from updated NCCN guideline for AML (version 1.2019 – January 18, 2019). The following criteria were removed regarding this diagnosis: 1) the patient is ≥ 75 years of age, and 2) according to the prescribing physician, the patient has comorbidities that preclude the use of intensive induction chemotherapy.	02/06/2018
Annual Revision	1. **Chronic Lymphocytic Leukemia:** The requirement of a trial of one prior therapy prior to approval was removed. 2. **Small Lymphocytic Lymphoma:** The requirement of a trial of one prior therapy prior to approval was removed. 3. **Mantle Cell Lymphoma:** For clarity, in criteria, the reference to Rituxan when listing previous required therapies was changed to "rituximab".	06/05/2019
Annual Revision	**The following changes were made:** 1. **Mantle Cell Lymphoma:** Wording of the criteria that states that patients are required to have tried at least one prior therapy had the caveat of "at least" added before it. Also, examples of therapies were moved from the criteria to a note. The example of RDHAX (rituximab, dexamethasone, cytarabine, oxaliplatin) was removed.	06/03/2020

NCCN – National Comprehensive Cancer Network; CLL – Chronic lymphocytic leukemia; FDA – Food and Drug Administration; SLL – Small lymphocytic leukemia; AML – Acute myeloid leukemia.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Verzenio Prior Authorization Policy

- Verzenio™ (abemaciclib tablets – Eli Lilly and Company)

REVIEW DATE: 02/24/2021

OVERVIEW

Verzenio, a cyclin-dependent kinase (CDK) 4/6 inhibitor, is indicated in hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative **advanced or metastatic breast cancer** in the following settings:[1]

- In combination with an aromatase inhibitor (AI) as initial endocrine-based therapy for the treatment of postmenopausal women.
- In combination with fulvestrant for the treatment of women with disease progression following endocrine therapy. Pre/perimenopausal women treated with Verzenio plus fulvestrant should be treated with a gonadotropin-releasing hormone (GnRH) agonist according to current clinical practice standards.
- As monotherapy for the treatment of adult patients with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on breast cancer (version 1.2021 – January 15, 2021) recommend any of the CDK4/6 inhibitors in combination with an AI or fulvestrant as a first-line preferred treatment option for recurrent or Stage IV HR+ and HER2-negative disease in postmenopausal women or premenopausal patient receiving ovarian ablation or suppression (category 1).[2,3] CDK4/6 inhibitor + fulvestrant is recommended for second- and subsequent-line therapy, if CDK4/6 inhibitor was not previously used (category 1). However, the guidelines also state in a footnote that if there

is disease progression on CDK4/6 inhibitor therapy or PI3K inhibitor, there are limited data to support an additional line of therapy with another CDK4/6-containing regimen.[2,4] For men with breast cancer, the compendium recommends they be treated similarly to postmenopausal women, except that the use of an AI is ineffective without concomitant suppression of testicular steroidogenesis.[3]

Supportive Data

A multicenter analysis evaluated clinical outcomes in patients (n = 58) with HR+/HER2-negative metastatic breast cancer who received Verzenio after disease progression on Ibrance (palbociclib tablets) or Kisqali (ribociclib tablets).[4] At data cutoff, 34% of patients (n = 20/58) had progressive disease, while 36% of patients (n = 21/58) had treatment duration exceeding 6 months. The median PFS was 5.8 months. Another case report of Verzenio use after 10 lines of therapy, including Ibrance therapy is available, along with literature review of ongoing studies with other CDK 4/6 inhibitors after prior use of another inhibitor.[5] Ibrance and Kisqali also have ongoing studies assessing for their respective efficacy after progression on another CDK4/6 inhibitor.[6,7] Preliminary results from the Kisqali trial (TRINITI-1), a Phase I/II, open-label trial of triplet therapy (Kisqali + everolimus + exemestane) after progression on prior CDK 4/6 inhibitor and up to three lines of therapy are available.[8] A total of 95 patients were evaluated; 41.1% of patients demonstrated clinical benefit, exceeding the predefined primary endpoint threshold (> 10%). The response rate was 8.4% and the median PFS was 5.7 months, and the 1-year PFS was 33%.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Verzenio. All approvals are provided for 3 years in duration unless otherwise noted below. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: a woman is defined as an individual with the biological traits of a woman, regardless of the individual's gender identity or gender expression; men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Verzenio is recommended in those who meet the following criteria:

FDA-Approved Indications

~~60.~~57. **Breast Cancer in Postmenopausal Women***. Approve for 3 years if the patient meets the following criteria (A, B, and C):

- **22.** Patient has advanced or metastatic hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND
- **23.** Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
- **24.** Patient meets ONE of the following criteria (i, ii, or iii):
  - **i.** Verzenio will be used in combination with anastrozole, exemestane, or letrozole; OR
  - **ii.** Verzenio will be used in combination with fulvestrant ; OR
  - **iii.** The patient meets the following conditions (a, b, and c):
    - **a)** Verzenio will be used as monotherapy; AND
    - **b)** Patient's breast cancer has progressed on at least one prior endocrine therapy; AND
      Note: Examples are anastrozole, exemestane, letrozole, tamoxifen, Fareston® [toremifene], exemestane plus everolimus, fulvestrant, everolimus plus fulvestrant or tamoxifen, megestrol acetate, fluoxymesterone, ethinyl estradiol.
    - **c)** Patient has tried chemotherapy for metastatic breast cancer.

***** Refer to the Policy Statement.

2. **Breast Cancer in Pre/Perimenopausal Women.*** Approve for 3 years if the patient meets the following criteria (A, B, C, and D):
   - **A)** Patient has advanced or metastatic hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND
   - **B)** Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
   - **C)** Patient is receiving ovarian suppression/ablation with a gonadotropin-releasing hormone (GnRH) agonist or has had surgical bilateral oophorectomy or ovarian irradiation; AND
     Note: Examples are Lupron (leuprolide), Trelstar (triptorelin), Zoladex (goserelin).
   - **D)** Patient meets ONE of the following conditions (i, ii, or iii):
     - **i.** Verzenio will be used in combination with anastrozole, exemestane, or letrozole; OR
     - **ii.** Verzenio will be used in combination with fulvestrant; OR
     - **iii.** Patient meets the following conditions (a, b, and c):
       - **a)** Verzenio will be used as monotherapy; AND
       - **b)** Patient's breast cancer has progressed on at least one prior endocrine therapy; AND
         Note: Examples are anastrozole, exemestane, letrozole, tamoxifen, Fareston® [toremifene], exemestane plus everolimus, fulvestrant, everolimus plus fulvestrant or tamoxifen, megestrol acetate, fluoxymesterone, ethinyl estradiol.
       - **c)** Patient has tried chemotherapy for metastatic breast cancer.

***** Refer to the Policy Statement.

Other Uses With Supportive Evidence

3. **Breast Cancer in Men*.** Approve for 3 years if the patient meets the following criteria (A, B, and C):
   - **D)** Patient has advanced or metastatic hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}]disease; AND
   - **E)** Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
   - **F)** Patient meets ONE of the following criteria (i, ii, or iii):
     - **i.** Patient meets BOTH of the following conditions (a and b):
       - **a)** Patient is receiving a gonadotropin-releasing hormone (GnRH) analog; AND
         Note: Examples are Lupron (leuprolide), Trelstar (triptorelin), Zoladex (goserelin), Firmagon (degarelix), Orgovyx (relugolix).
       - **b)** Verzenio will be used in combination with anastrozole, exemestane, or letrozole; OR
     - **ii.** Verzenio will be used in combination with fulvestrant; OR
     - **iii.** Patient meets the following conditions (a, b, and c):
       - **a)** Verzenio will be used as monotherapy; AND
       - **b)** Patient's breast cancer has progressed on at least one prior endocrine therapy; AND
         Note: Examples are anastrozole, exemestane, letrozole, tamoxifen, Fareston (toremifene), exemestane plus everolimus, fulvestrant, everolimus plus fulvestrant or tamoxifen, megestrol acetate, fluoxymesterone, ethinyl estradiol.
       - **c)** Patient has tried chemotherapy for metastatic breast cancer**.**

***** Refer to the Policy Statement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Verzenio is not recommended in the following situations:

260. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Verzenio™ tablets [prescribing information]. Indianapolis, IN: Eli Lilly and Company; March 2020.
2. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 1.2021 – January 15, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 21, 2021.
3. The NCCN Drugs & Biologics Compendium. © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 21, 2021. Search terms: abemaciclib.
4. Wander SA, Zangardi M, Niemierko A, et al. A multicenter analysis of abemaciclib after progression on palbociclib in patients (pts) with hormone-receptor-positive (HR+)/HER2- metastatic breast cancer (MBC). *J Clin Oncol*. 2019;37:15_suppl, 1057-1057.
5. Wender IO, Haines K, Jahanzeb M. Response to abemaciclib after 10 lines of therapy including palbociclib in metastatic breast cancer: a case report with literature review. *Oncol Ther*. 2020;8:351-358.
6. Novartis Pharmaceuticals. Study of ribociclib with everolimus + exemestance in HR+ HER2- locally advanced/metastatic breast cancer post progression on CDK 4/6 inhibitor. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2021 Feb 21]. Available at: https://www.clinicaltrials.gov/ct2/show/NCT02732119?term=02732119&draw=2&rank=1. NLM Identifier: NCT02732119.
7. Dana-Farber Cancer Institute, Pfizer. Palbociclib after CDK and endocrine therapy (PACE). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2021 Feb 21]. Available at: https://www.clinicaltrials.gov/ct2/show/NCT03147287?term=03147287&draw=2&rank=1. NLM Identifier: NCT03147287.
8. Bardia A, Hurvitz SA, DeMichele A, et al. Triplet therapy (continuous ribociclib, everolimus, exemestane) in HR+/HER2- advanced breast cancer postprogression on a CDK4/6 inhibitor (TRINITI-1): efficacy, safety, and biomarker results. Abstract 1016. *J Clin Oncol.* 2019;37(15):1016-1016.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Deleted requirement in all conditions that Verzenio + aromatase inhibitor use should be in first-line setting. For use of Verzenio + Faslodex, deleted requirement to try a prior endocrine therapy since guidelines recommend first-line use. In the monotherapy criteria, re-worded to state patient has progressed on at least one prior endocrine therapy and changed the list of endocrine therapies to examples.	04/03/2019
Annual Revision	Limited data are available that Verzenio can be used after the patient has progressed on Ibrance or Kisqali. Due to this, the criteria "The patient has not had disease progression while on Verzenio, Ibrance, or Kisqali" has been modified to state "The patient has not had disease progression while on Verzenio."	04/15/2020
Early Annual Revision	**All Breast Cancer Indications:** Deleted criteria requiring no disease progression on Verzenio, based on guidelines and available data. **Breast Cancer in Pre/Perimenopausal Women:** Examples of gonadotropin-releasing hormone (GnRH) agonists are moved from criteria to Note. **Breast Cancer in Men:** GnRH "agonist" is changed to "analog". Also, the list of examples of GnRH analog agents are moved from criteria to Note. Firmagon (degarelix) and Orgovyx (relugolix) were added to example list.	02/24/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Vistogard Prior Authorization Policy

- Vistogard® (uridine triacetate oral granules – Wellstat Therapeutics)

REVIEW DATE: 07/29/2020

OVERVIEW

Vistogard, a pyrimidine analog, is indicated for the emergency treatment of adult and pediatric patients:

- Following a fluorouracil or capecitabine overdose regardless of the presence of symptoms; or
- Who exhibit early-onset, severe or life-threatening toxicity affecting the cardiac or central nervous system, and/or early-onset, unusually severe adverse reactions (e.g., gastrointestinal toxicity, neutropenia) within 96 hours following the end of fluorouracil or capecitabine administration.[1]

As a limitation of use, Vistogard is not recommended for the non-emergent treatment of adverse events associated with fluorouracil or capecitabine because it may diminish the efficacy of these drugs.[1] Additionally, the safety and efficacy of Vistogard initiated more than 96 hours following the end of fluorouracil or capecitabine administration have not been established. Vistogard is supplied in 10 gram packets. For adults, the dose is 10 grams (1 packet) every 6 hours for 20 doses. For pediatric patients, the dose is 6.2 grams/m^2 of body surface area (not to exceed 10 grams per dose) every 6 hours for 20 doses. Any unused portion of a packet must be discarded; it should not be saved for subsequent doses.

Disease Overview

Fluorouracil and capecitabine (a fluorouracil prodrug) are widely used chemotherapeutic agents with potential for significant toxicity. Exaggerated sensitivity to capecitabine or fluorouracil may occur due to genetic variations in certain enzymes, renal impairment, or other causes.[2] Toxicity results in tissue damage, often manifesting as ulcerative mucositis with neutropenia leading to sepsis, shock, and organ failure. Additionally, central neurotoxicity and cardiac toxicity may occur without any identifiable predisposing factors. Exogenous uridine competes with the toxic metabolite fluorouridine triphosphate for incorporation into RNA in normal tissues, thereby protecting the tissues from toxicity.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Vistogard. All approvals are provided for the duration noted below.

Automation: None

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vistogard is recommended in those who meet the following criteria:

FDA-Approved Indications

26. Capecitabine or Fluorouracil Overdose. Approve for 7 days.

27. Capecitabine or Fluorouracil Toxicity, Severe or Life-Threatening. Approve for 7 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vistogard is not recommended in the following situations:

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

401. Vistogard® oral granules [prescribing information]. Rockville, MD: Wellstat Therapeutics; February 2017.
402. Ma WW, Saif MW, El-Rayes BF, et al. Emergency use of uridine triacetate for the prevention and treatment of life-threatening 5-fluorouracil and capecitabine toxicity. *Cancer*. 2017;123(2):345-356.

HISTORY

Type of Revision	Summary of Changes	Review Date
New policy	--	08/07/2019
Annual Revision	No changes to criteria.	07/29/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Vitrakvi Prior Authorization Policy

- Vitrakvi® (larotrectinib capsules and oral solution – Loxo Oncology/Bayer)

REVIEW DATE: 12/16/2020

OVERVIEW

Vitrakvi, a kinase inhibitor, is indicated for the treatment of adult and pediatric patients with **solid tumors** that: have a **neurotrophic receptor tyrosine kinase (NTRK) gene fusion** without a known acquired resistance mutation; are metastatic or where surgical resection is likely to result in severe morbidity; and have no satisfactory alternative treatments or that have progressed following treatment.[1]

Guidelines/Compendium

The National Comprehensive Cancer Network (NCCN) Compendium lists the following cancers as recommended uses for Vitrakvi:[2] breast cancer, cervical cancer, esophageal and esophagogastric cancer, gastric cancer, gastrointestinal stromal tumors (GISTs), extra and intrahepatic cholangiocarcinoma, gallbladder cancer, hepatocellular carcinoma, soft tissue sarcoma, uterine sarcoma, endometrial carcinoma, small bowel adenocarcinoma, angiosarcoma, rhabdomyosarcoma, retroperitoneal/intra-abdominal sarcoma, salivary gland tumors, cutaneous melanoma, central nervous system cancers, thyroid carcinoma, rectal cancer, non-small cell lung cancer, colon cancer, ovarian cancer, pancreatic cancer, and vulvar cancer (squamous cell carcinoma).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vitrakvi. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vitrakvi is recommended in those who meet the following criteria:

FDA-Approved Indications

2. **Solid Tumors.** Approve for 3 years if the patient meets the following criteria (A, B, and C):
   A) Patient's tumor has a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation; AND

B) Patient meets one of the following criteria (i or ii):
- **i.** The tumor is metastatic; OR
- **ii.** Surgical resection of tumor will likely result in severe morbidity; AND

C) Patient meets one of the following criteria (i or ii):
- **i.** There are no satisfactory alternative treatments; OR
- **ii.** Patient has disease progression following treatment.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Vitrakvi is not recommended in the following situations:

261. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

403. Vitrakvi® capsules and oral solution [prescribing information]. Stamford, CT: Loxo Oncology, Inc.; November 2018.
404. The NCCN Drugs & Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 14, 2020. Search terms: larotrectinib.

HISTORY
Type of Revision	Summary of Changes	Review Date
New Policy	--	11/28/2018
Annual Revision	No criteria changes.	12/04/2019
Annual Revision	No criteria changes.	12/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Vizimpro Prior Authorization Policy
- Vizimpro® (dacomitinib tablets – Pfizer Labs)

REVIEW DATE: 10/21/2020

OVERVIEW
Vizimpro, a kinase inhibitor, is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.[1]

Guidelines
The National Comprehensive Cancer Network (NCCN) guidelines for NSCLC (version 8.2020 – September 15, 2020) recommends Vizimpro, Tarceva® (erlotinib tablets), Iressa® (gefitinib tablets), Gilotrif™ (afatinib tablets) and Tagrisso™ (osimertinib tablets) [all category 1] for the first-line treatment of patients with sensitizing *EGFR*-mutation positive NSCLC discovered before first-line chemotherapy.[2] Tagrisso is noted as the "preferred" option; whereas the rest of the agents are "Other Recommended" first-line therapies. Upon disease progression, T790M testing is recommended. Tagrisso is a category 1 recommended option if T790M mutation-positive. Patients can also continue Vizimpro, Tarceva, Gilotrif, or Iressa (category 2A).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Vizimpro. All approvals are provided for 3 years in duration as noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vizimpro is recommended in those who meet the following criteria:

FDA-Approved Indications

~~61.~~58. **Non-Small Cell Lung Cancer (NSCLC) – Epidermal Growth Factor Receptor (EGFR) Mutation-Positive.** Approve for 3 years if the patient meets the following criteria (A and B):

~~25.~~ Patient has *metastatic* NSCLC; AND

~~26.~~ Patient meets ONE of the following criteria (i or ii):

- **i.** Patient has epidermal growth factor receptor (EGFR) exon 19 deletion as detected by an approved test; OR
- **ii.** Patient has exon 21 (L858R) substitution mutations as detected by an approved test.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vizimpro is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Vizimpro® tablets [prescribing information]. New York, NY: Pfizer Labs; September 2018.
2. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 8.2020 – September 15, 2020) © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed October 21, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	New Criteria	10/03/2018
Annual Revision	No criteria changes	10/02/2019
Annual Revision	No criteria changes	10/21/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Votrient® (pazopanib tablets – GlaxoSmithKline)

DATE REVIEWED: 05/27/2020

OVERVIEW

Votrient, a multi-tyrosine kinase inhibitor, is indicated for the treatment of patients with advanced renal cell carcinoma (RCC), and for the treatment of patients with advanced soft tissue sarcoma (STS) who have received prior chemotherapy.[1] Limitation of Use. The efficacy of Votrient for the treatment of patients with adipocytic STS or gastrointestinal stromal tumors (GIST) has not been demonstrated.

Guidelines

Votrient features prominently in the National Comprehensive Cancer Network (NCCN) guidelines for soft tissue sarcomas and kidney cancer and others. The indications listed in the FDA-approved and Other Uses with Supportive Evidence sections are supported by the prescribing information and/or the NCCN Compendium/Guidelines.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Votrient. All approvals are provided for 3 years in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Votrient is recommended in those who meet the following criteria:

FDA-Approved Indications

~~62.~~59. **Renal Cell Carcinoma** (Clear Cell or Non-Clear Cell Histology). Approve for 3 years for relapsed or Stage IV disease.

2. **Soft Tissue Sarcoma (STS).** Approve for 3 years if the patient meets the following criteria (A, B, and C):
   - **A)** The soft tissue sarcoma is advanced or metastatic; AND
   - **B)** The patient has ONE of the following (i, ii, iii, iv, v, or vi):[3]
     - **i.** Angiosarcoma; OR
     - **ii.** Pleomorphic rhabdomyosarcoma; OR
     - **iii.** Retroperitoneal/intra-abdominal soft tissue sarcoma that is unresectable or progressive; OR
     - **iv.** Soft tissue sarcoma of the extremity/superficial trunk or head/neck, including synovial sarcoma; OR
     - **v.** Solitary fibrous tumor/hemangiopericytoma; OR
     - **vi.** Alveolar soft part sarcoma; OR
   - **C)** The patient does not have gastrointestinal stromal tumor (GIST) [see Criterion 4].

Other Uses with Supportive Evidence

3. **Differentiated (i.e., papillary, follicular, and Hürthle cell) Thyroid Carcinoma.** Approve for 3 years if refractory to radioactive iodine therapy.

4. **Gastrointestinal Stromal Tumor (GIST).** Approve for 3 years if the patient meets the following criteria (A, B, and C):
   - **I)** Patient has previously tried imatinib (Gleevec® tablets, generics); AND
   - **J)** Patient has previously tried Sutent® (sunitinib capsules); AND
   - **K)** Patient has previously tried Stivarga® (regorafinib tablets).

5. **Medullary Thyroid Carcinoma.** Approve for 3 years if the patient has tried Caprelsa® (vandetanib tablets) or Cometriq® (cabozantinib capsules).

6. **Ovarian Cancer (i.e., Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer).** Approve for 3 years if the patient has persistent or recurrent disease.

7. **Uterine Sarcoma (e.g., endometrial stromal sarcoma, undifferentiated uterine sarcoma, uterine leiomyosarcomas).** Approve for 3 years in patients with recurrent, advanced, or metastatic disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Votrient has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below.

262. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

405. Votrient® tablets [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; May 2017.
406. The NCCN Drugs & Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 25, 2020. Search term: pazopanib.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Annual revision	Soft Tissue Sarcoma: Head/neck was added to the list of indications. Ovarian Cancer: Criteria were revised to add patients with persistent or recurrent disease.	03/08/2017
Annual revision	• Dermatofibrosarcoma Protuberans: This indication was removed. The NCCN guidelines no longer recommend this use. • Uterine sarcoma: "Recurrent" was added to the criteria.	04/18/2018
Annual revision	• Renal Cell Carcinoma: Deleted "advanced" and "predominant" descriptor with regards to clear cell. Added patient has "relapsed or Stage IV disease". • Soft Tissue Sarcoma: Added Alveoloar soft part sarcoma and Solitary fibrous tumor/hemeangiopericytoma. Deleted "Other non-lipogenic soft tissue sarcoma. • Ovarian Cancer: Deleted criteria requiring patient to have complete clinical remission after prior chemotherapy. • Deleted all conditions listed under "Conditions Not Recommended for Approval".	05/08/2019
Annual revision	• No criteria changes	05/27/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Xalkori Prior Authorization Policy
- Xalkori® (crizotinib capsules – Pfizer)

REVIEW DATE: 12/16/2020; 01/27/2021 selected revision

OVERVIEW

Xalkori, an oral kinase inhibitor, is indicated for the treatment of patients with:[1]

- **Non-small cell lung cancer (NSCLC)**, whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.
- **NSCLC,** metastatic, whose tumors are ROS1-positive.
- **Anaplastic large cell lymphoma (ALCL)**, treatment of pediatric patients ≥ 1 year of age and young adults with relapsed or refractory, systemic ALCL that is *ALK*-positive.
  Limitations of Use: The safety and efficacy of Xalkori have not been established in older adults with relapsed or refractory, systemic *ALK*-positive ALCL.

Rearrangements involving the ALK locus on chromosome 2p33 have been documented in approximately 50% of inflammatory myofibroblastic tumors (IMTs).[7] IMTs occur primarily during the first two decades of life and typically arise in the lung, retroperitoneum, or abdominal region. Sustained partial response to Xalkori in a patient *with* ALK-translocated IMT, and no observed activity in a patient *without* ALK translocation have been reported. In another case report, a 45-year old Hispanic female was eventually diagnosed to have IMT with systemic involvement and ALK gene rearrangement.[8] The patient was treated with Xalkori and had a successful resolution of her lesions and symptoms. After a 27-month follow-up, the patient remained in complete clinical and radiologic remission.

Guidelines

According to the National Comprehensive Cancer Network (NCCN) guidelines:

- **NSCLC** (version 1.2021 – November 25, 2020), Alecensa® (alectinib capsules) is the preferred therapy (category 1).[2,5] Other recommended therapies include Zykadia™ (ceritinib capsules) and Alunbrig™ (brigatinib tablets) [both also category 1]. Xalkori (category 1 as well) is listed as Useful in Certain Circumstances. For subsequent therapy with progression on Xalkori, therapy can be switched to Zykadia, Alecensa, or Alunbrig (if not previously given) [all category 2A]. For

progression on Alecensa, Alunbrig, or Zykadia, Lorbrena (lorlatinib tablets) is recommended (category 2A). Xalkori (Preferred) or Zykadia (Other Recommended therapy) are recommended as first-line therapy for ROS1 rearrangement-positive NSCLC (both category 2A). Lorbrena can be used as subsequent therapy for ROS1 rearrangement. Xalkori is also recommended as an emerging targeted therapy in patients with high level *MET* amplification or *MET* exon 14 skipping mutation in lung cancer (category 2A).

- **Soft tissue sarcoma** guidelines (version 1.2021 – October 30, 2020) recommend Xalkori as single-agent therapy for the treatment of IMT with ALK translocation (category 2A recommendation).[3,5]
- **T-Cell lymphoma** guidelines (version 1.2021 – October 5, 2020) recommend Xalkori use in ALK-positive anaplastic large cell lymphoma (ALCL) as a second-line and subsequent therapy option (category 2A) in patients with intent to proceed to transplant and in those who do not intend to proceed to transplant.[4,5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Xalkori. All approvals are provided for 3 years unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xalkori is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Non-Small Cell Lung Cancer (NSCLC).** Approve for 3 years if the patient has metastatic anaplastic lymphoma kinase (ALK)-positive NSCLC as detected by an approved test.

2. **Non-Small Cell Lung Cancer (NSCLC) with ROS1 Rearrangement.** Approve for 3 years if the patient has recurrent or metastatic disease as detected by an approved test.

3. **Anaplastic Large Cell Lymphoma.** Approve for 3 years if the patient meets the followring criteria (A, B, and C):
   - **A)** Patient were ≥ 1 year of age and ≤ 21 years of age; AND
   - **B)** Patient has anaplastic lymphoma kinase (*ALK*)-positive disease; AND
   - **C)** Patient has received at least one prior systemic treatment regimen.
     Note: Examples of systemic treatment were Adcetris (brentuximab vendotin for injection) in combination with CHP (cyclophosphamide, doxorubicin, and prednisone), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone).

Other Uses with Supportive Evidence

4. **Non-Small Cell Lung Cancer (NSCLC) with High Level *MET* Amplification or MET Exon 14 Skipping Mutation.** Approve for 3 years.

5. **Soft Tissue Sarcoma – Inflammatory Myofibroblastic Tumor (IMT) with ALK Translocation.** Approve for 3 years.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xalkori is not recommended in the following situations:

263. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

327. Xalkori® capsules [prescribing information]. New York, NY: Pfizer Inc; January 2021.
328. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 1.2021 – November 25, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 14, 2020.
329. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (version 1.2021 – October 30, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 14, 2020.
330. The NCCN T-Cell lymphomas Clinical Practice Guidelines in Oncology (version 1.2021 – October 5, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed January 25, 2021.

331. The NCCN Drugs & Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on: December 14, 2020. Search term: crizotinib.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	12/19/2018
Annual Revision	For ROS1 rearrangement, added "if the patient has recurrent or metastatic disease as detected by an approved test. For Peripheral T-Cell Lymphoma indication, deleted phrases "a single agent for second-line" and "in patients with intention to proceed and no intention to proceed to transplant." Added "for relapsed or refractory disease."	12/18/2019
Annual Revision	No criteria changes.	12/16/2020
Selected Revision	**Anaplastic Large Cell Lymphoma:** Added new approval condition and criteria based on FDA-approval and guidelines. **Peripheral T-Cell Lymphoma – Anaplastic Large Cell Lymphoma (ALCL), ALK-Positive:** Deleted this approval condition and criteria from Other Uses with Supportive Evidence, now that is addressed as an FDA-approved indication.	01/27/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Xermelo™ (telotristat ethyl tablets – Lexicon Pharmaceuticals)

DATE REVIEWED: 05/13/2020

OVERVIEW

Xermelo is indicated for the treatment of carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy.[1] Telotristat, the active metabolite, inhibits tryptophan hydroxylase, which mediates the rate limiting step in serotonin biosynthesis. Serotonin plays a role in mediating secretion, motility, inflammation, and sensation of the gastrointestinal tract and is overproduced in patients with carcinoid syndrome. Xermelo specifically reduces the production of peripheral serotonin and decreases the frequency of carcinoid syndrome diarrhea. The inclusion criteria for the TELESTAR pivotal study required all patients randomized to Xermelo or placebo groups to have at least four bowel movements per day while on SSA therapy.[2] The study also required patients to be receiving a stable-dose of SSA therapy for at least 3 months prior to trial enrollment.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Xermelo. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xermelo is recommended in those who meet the following criteria:

FDA-Approved Indications

~~63.~~60. Carcinoid Syndrome Diarrhea.

A) Initial Therapy. Approve for 3 years if the patient meets all of the following criteria (i, ii, and iii):

i. The patient has been on a long-acting somatostatin analog (SSA) therapy for at least 3 consecutive months.
Note: Examples of long-acting SSA therapy are Somatuline® Depot (lanreotide for injection), Sandostatin® LAR Depot (octreotide for injection); AND

ii. While on a long-acting somatostatin analog therapy (prior to starting Xermelo), the patient continues to have at least four bowel movements per day; AND

iii. Xermelo will be used concomitantly with a long-acting somatostatin analog therapy.

B) Patient is Currently Receiving Xermelo. Approve for 3 years if the patient is continuing to take Xermelo concomitantly with a long-acting somatostatin analog therapy for carcinoid syndrome diarrhea.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Xermelo has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

264. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

332. Xermelo™ tablets [prescribing information]. The Woodlands, TX: Merck; February 2017.
333. Kulke MH, Horsch D, Caplin ME, et al. Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. *J Clin Oncol.* 2017;35:14-23.

HISTORY

Type of Revision	Summary of Changes*	Date Reviewed
New Policy	New criteria	03/08/2017
Annual revision	No criteria changes	04/04/2018
Annual revision	No criteria changes	04/17/2019
Annual revision	No criteria changes	05/13/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Xospata Prior Authorization Policy

- Xospata® (gilteritinib tablets – Astellas)

REVIEW DATE: 12/02/2020

OVERVIEW

Xospata, an inhibitor of tyrosine kinases including FMS-like tyrosine-kinase 3 (FLT3), is indicated for the treatment of relapsed or refractory **acute myeloid leukemia** (AML) in adults with an FLT3 mutation as detected by an FDA-approved test.[1]

Disease Overview

AML is a heterogeneous hematologic malignancy that is hallmarked by clonal expansion of myeloid blasts in the peripheral blood, bone marrow, and/or other tissues.[2] It is a rather common form of acute leukemia in adults and it has the largest number of annual deaths from leukemias in the US. Around 19,940 people will be diagnosed with AML in 2020, and 11,180 patients will die from the condition. The median age at diagnosis is 68 years of age. Over one-half and approximately one-third of patients receive the diagnosis at ≥ 65 and ≥ 75 years of age, respectively. The incidence of AML, along with myelodysplastic syndrome (MDS) is rising as patients become older. Environmental factors play a role and include prolonged exposure to petrochemicals; solvents such as benzene; pesticides, and

ionizing radiation. Also, two cytotoxic agents that are associated with therapy-related MDS/AML are alkylating agents (e.g., cyclophosphamide) and topoisomerase inhibitors (e.g., doxorubicin). Antimetabolite therapy, notably fludarabine, has also been associated with MDS/AML in patients with lymphoproliferative disorders, especially when given in combination with alkylating agents. Treatment of AML can involve the following modalities at various stages: chemotherapy, radiation therapy, chemotherapy with stem cell transplant, and other drug therapy. Molecular or karyotypic abnormalities can also be identified, of which FLT3 is noted. The two major classes of activating FLT3 mutations are internal tandem duplications (ITD) and tyrosine kinase domain (TKD) point mutations. FLT3-ITD mutations occur in around 30% of cases and are more common than FLT3-TKD mutations, which occur in approximately 10% of patients. Prognosis can be worse in patients with certain types of FLT3 mutations (e.g. shorter remissions, decreased overall survival).

Guidelines

The National Comprehensive Cancer Network (NCCN) has various guidelines that address Daurismo.[2,3]

- **Acute Myeloid Leukemia:** NCCN guidelines for AML (version 2.2021- November 12, 2020) recommended Xospata in patients ≥ 18 years of age for therapy for relapsed or refractory disease for patients with the FLT3-ITD and FLT3-TKD mutation (category 1 for both).[2]
- **Myeloid/Lymphoid Neoplasms:** NCCN guidelines for myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase fusion genes (version 3.2021 – August 21, 2020) recommend Xospata in various clinical scenarios involving lymphoid, myeloid or mixed lineage neoplasms with eosinophilia and FLT3 rearrangement (category 2A).[3]

Safety

Xospata has a Boxed Warning regarding differential syndrome, which can be fatal if not treated. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until resolution of symptoms.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Xospata. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xospata is recommended in those who meet the following criteria:

FDA-Approved Indications

147. Acute Myeloid Leukemia (AML). Approve for 3 years if the patient meets the following criteria (A, B, and C).
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has relapsed or refractory disease; AND
- **C)** Disease is *FLT3*-mutation positive as detected by an approved test.

Other Uses with Supportive Evidence

148. Lymphoid, Myeloid, or Mixed Lineage Neoplasms. Approve for 3 years if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has eosinophilia; AND
- **C)** Disease is *FLT3*-mutation positive as detected by an approved test.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xospata is not recommended in the following situations:

157. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available Condition.

REFERENCES

497. Xospata® tablets [prescribing information]. Northbrook, IL: Astellas Pharma; May 2019.
498. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (version 2.2021 – November 12, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on November 23, 2020.
499. The NCCN Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes Clinical Practice Guidelines in Oncology (version 3.2021 – August 21, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on November 23, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	Not applicable.	11/30/2018
Annual Revision	No criteria changes.	12/04/2019
Annual Revision	**Acute Myeloid Leukemia:** Added criteria that the patient is ≥ 18 years of age per National Comprehensive Cancer Network criteria and the FDA-approval age threshold. **Lymphoid, Myeloid, or Mixed Lineage Neoplasms:** Added new criteria in the "Other Uses with Supportive Evidence" section to approve for 3 years per guidance from National Comprehensive Cancer Network guidelines for patients ≥ 18 years of age with eosinophilia and have disease that is FLT3-mutation positive as detected by an approved test.	12/02/2020

FLT3 – FMS-like tyrosine kinase 3.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Xospata® (gilteritinib tablets – Astellas)

DATE REVIEWED: 12/04/2019

OVERVIEW

Xospata, an inhibitor of tyrosine kinases including FMS-like tyrosine-kinase 3 (FLT3), is indicated for the treatment of adults who have relapsed or refractory acute myeloid leukemia (AML) with a FLT3 mutation as detected by an FDA-approved test.[1] The recommended initial dose is 120 orally once daily (QD). Response may be delayed. In the absence of disease progression or unacceptable toxicity, treatment for a minimum of 6 months is recommended to allow time for a clinical response. Dosage modifications are recommended for patients who experience toxicities related to Xospata.

Disease Overview

AML is a heterogeneous hematologic malignancy that is hallmarked by clonal expansion of myeloid blasts in the peripheral blood, bone marrow, and/or other tissues.[2] It is a rather common form of acute leukemia in adults and it has the largest number of annual deaths from leukemias in the US. Around 21,450 people will be diagnosed with AML in 2019, and 10,920 patients will die from the condition. The median age at diagnosis is 67 years. Over one-half and approximately one-third of patients receive the diagnosis at ≥ 65 and ≥ 75 years of age, respectively. The incidence of AML, along with myelodysplastic syndrome (MDS) is rising as patients become older. Environmental factors play a role and include prolonged exposure to petrochemicals; solvents such as benzene; pesticides, and ionizing radiation. Also, two cytotoxic agents that are associated with therapy-related MDS/AML are alkylating agents (e.g., cyclophosphamide) and topoisomerase inhibitors (e.g., doxorubicin). Antimetabolite therapy, notably

fludarabine, has also been associated with MDS/AML in patients with lymphoproliferative disorders, especially when given in combination with alkylating agents. Treatment of AML can involve the following modalities at various stages: chemotherapy, radiation therapy, chemotherapy with stem cell transplant, and other drug therapy. Molecular or karyotypic abnormalities can also be identified, of which FLT3 is noted. The two major classes of activating FLT3 mutations are internal tandem duplications (ITD) and tyrosine kinase domain (TKD) point mutations. FLT3-ITD mutations occur in around 30% of cases and are more common than FLT3-TKD mutations, which occur in approximately 10% of patients. Prognosis can be worse in patients with certain types of FLT3 mutations (e.g. shorter remissions, decreased overall survival).

Clinical Efficacy

The efficacy of Xospata was evaluated in a trial called ADMIRAL, which involved adults with relapsed or refractory AML having a FLT3, ITD, D835, or 1836 mutation.[1,3] The first interim analysis of the trial involved 138 patients.[1] The median follow-up was 4.6 months. Among the 106 patients who were dependent on red blood cell and/or platelet transfusions at baseline, approximately 31% of patients became independent of RBC and platelet transfusions during any 56-day post-baseline period. The rate of complete remission (CR)/complete remission with partial hematologic recovery (CR/CRh) was 21% (n = 29/138). The final analysis involved 371 patients who received Xospata 120 mg QD (n = 247) over continuous 28-day cycles or a prespecified chemotherapy regimen (n = 124) which included high intensity combinations (MEC [mitoxantrone, etoposide, and cytarabine] and FLAG-IDA [fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin) and low intensity regimens (LDAC [low-dose cytarabine] and AZA [azacitidine]). At the time of analysis, the median follow-up was 17.8 months. Patients who received Xospata had a significant longer survival compared with patients given chemotherapy (hazard ratio 0.64; 95% confidence interval: 0.49, 0.83; P = 0.0004).

Guidelines

The National Comprehensive Cancer Network (NCCN) has guidelines for AML (version 2.2020 – September 3, 2019) are extensive.[2] Many medications are utilized at various stages of patients with AML. For relapsed or refractory disease, Xospata is a recommended therapy for AML among patients with an FLT3-ITD mutation (category 1). Hypomethylating agents (azacitidine or decitabine) plus Nexavar® (sorafenib tablets) are also recommended for patients with an FLT3-ITD mutation (category 2A). For patients with AML with an FLT3-TKD mutation, Xospata is recommended (category 1).

Safety

Xospata has a Boxed Warning regarding differential syndrome, which can be fatal if not treated. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until resolution of symptoms.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Xospata. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xospata is recommended in those who meet the following criteria:

FDA-Approved Indications

149. Acute Myeloid Leukemia (AML). Approve for 3 years if the patient meets the following criteria (A and B).
- **A)** The patient has relapsed or refractory disease; AND
- **B)** The disease is *FLT3*-mutation positive as detected by an approved test.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Xopsata has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

158. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available Condition.

REFERENCES

500. Xospata® tablets [prescribing information]. Northbrook, IL: Astellas Pharma; May 2019.
501. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (Version 2.2020 – September 3, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on November 29, 2019.
502. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory *FLT3*-mutated AML. *N Engl J Med*. 2019;381:1728-1740.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	Not applicable.	11/30/2018
Annual revision	No criteria changes.	12/04/2019

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Xpovio Prior Authorization Policy

- Xpovio™ (selinexor tablets – Karyopharm Therapeutics)

REVIEW DATE: 02/03/2021

OVERVIEW

Xpovio, a nuclear export inhibitor, is indicated for treatment of the following conditions:[1]

- **Diffuse large B-cell lymphoma** (DLBCL), not otherwise specified (including DLBCL arising from follicular lymphoma), for treatment of adults with relapsed or refractory disease, after at least two lines of systemic therapy.
- **Multiple myeloma**:
  - In combination with dexamethasone for adults with relapsed or refractory disease who have received at least four prior therapies and whose disease is refractory to at least two proteasomes inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.
  - In combination with bortezomib and dexamethasone, in adults who have received at least one prior therapy.

For both of these indications, Xpovio was approved under accelerated approval based on response rate. Continued approval may be contingent upon verification in a confirmatory trial.

Guidelines

Xpovio is addressed in the following guidelines from the National Comprehensive Cancer Network (NCCN):

- **B-Cell Lymphoma:** NCCN guidelines (version 1.2021 – January 20, 2021) recommend Xpovio as third-line and subsequent therapy of DLBCL, after at least two lines of systemic therapy.[3]
- **Multiple Myeloma:** NCCN guidelines (version 4.2021 – December 10, 2020) recommend various regimens as primary therapy (transplant eligible and non-transplant candidates), maintenance therapy, and previously treated multiple myeloma.[2] Xpovio/bortezomib/dexamethasone is among the other recommended regimens for previously treated disease. Xpovio/dexamethasone (specifically for the approved indication), Xpovio/Darzalex (daratumumab injection)/dexamethasone, and Xpovio/Pomalyst (pomalidomide capsules)/dexamethasone are among the regimens considered useful in certain circumstances for previously treated multiple myeloma.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Xpovio. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xpovio is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Diffuse Large B-Cell Lymphoma.** Approve for 3 years if the patient meets BOTH of the following (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has been treated with at least two prior systemic therapies.

2. **Multiple Myeloma.** Approve for 3 years if the patient meets ALL of the following (A, B, and C):
   - **5.** Patient is ≥ 18 years of age; AND
   - **6.** The medication will be taken in combination with dexamethasone; AND
   - **7.** Patient meets one of the following (i, ii, or iii):
     - **A)** Patient has tried at least four prior regimens for multiple myeloma; OR
     - **B)** Patient meets both of the following (a and b):
       - **i.** Patient has tried at least one prior regimen for multiple myeloma; AND
       - **ii.** The medication will be taken in combination with bortezomib; OR
     - **C)** Patient meets both of the following (a and b):
       - **i.** Patient has tried at least one prior regimen for multiple myeloma; AND
       - **ii.** The medication will be taken in combination with Darzalex (daratumumb infusion), Darzlaex Faspro (daratumumab and hyaluronidase-fihj injection), or Pomalyst (pomalidomide capsules).

     Note: Examples include bortezomib/Revlimid (lenalidomide capsules)/dexamethasone, Kyprolis (carfilzomib infusion)/Revlimid/dexamethasone, Darzalex (daratumumab injection)/bortezomib or Kyprolis/dexamethasone, or other regimens containing a proteasome inhibitor, immunomodulatory drug, and/or anti-CD38 monoclonal antibody.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xpovio is not recommended in the following situations:

159. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

503. Xpovio [prescribing information]. Newton, MA: Karyopharm Therapeutics; December 2020.
504. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (version 4.2021 – December 10, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 31, 2021.
505. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 1.2021 – January 20, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 31, 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/08/2019
Annual Revision	**Diffuse B-Cell Lymphoma:** This newly approved indication was added as a 3-year approval, if the patient is ≥ 18 years of age, and if the patient has tried at least two prior systemic therapies. **Multiple Myeloma:** Criteria were added to require that the patient is ≥ 18 years of age, and that Xpovio be prescribed in combination with dexamethasone. This is aligned with the FDA-approved labeling. Sarclisa and Darzalex Faspro were added as examples of anti-CD38 monoclonal antibodies which may have been tried prior to Xpovio.	07/01/2020
Update	07/10/2020: No criteria changes. Overview was updated to include NCCN recommendations for diffuse large B-cell lymphoma.	N/A
Early Annual Revision	**Multiple Myeloma:** Criteria were added to approve in the second-line setting, if the patient is ≥ 18 years of age, patient has tried one previous regimen, and Xpovio will be taken in combination with dexamethasone and one of the following medications: bortezomib, Darzalex (daratumumb infusion), Darzlaex Faspro (daratumumab and hyaluronidase-fihj injection), or Pomalyst (pomalidomide capsules). For use in the fifth-line setting, criteria were changed to require at least four prior regimens for multiple myeloma, with examples of regimens listed in a note. Previously, criteria specified which mechanisms of action must have been in the regimens and included two proteasome inhibitors, two immunomodulatory drugs, and an anti-CD-38 monoclonal antibody.	02/03/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Xtandi® (enzalutamide capsules – Astellas Pharma/Catalent Pharma Solutions/Medivation)

DATE REVIEWED: 03/04/2020

OVERVIEW

Xtandi is an androgen receptor inhibitor indicated for the treatment of patients with castration-resistant prostate cancer (CRPC).[1] It is also indicated for the treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC). Patients should receive Xtandi with a concurrent gonadotropin-releasing hormone (GnRH) analog or should have had a bilateral orchiectomy.

Guidelines

According to the NCCN guidelines on prostate cancer (version 4.2019 – August 19, 2019), all patients with mCRPC should maintain castrate levels of serum testosterone (< 50 ng/dL) and receive best supportive care.[2] Erleada™ (apalutamide tablets), Nubeqa (darolutamide tablets), and Xtandi are all category 1 recommended options for non-metastatic CRPC (M0) especially if the prostate specific antigen doubling time (PSADT) ≤ 10 months.

- For patients who progress to CRPC and are positive for distant metastasis, M1, and there are no visceral metastases, Zytiga® (abiraterone acetate tablets) and prednisone, docetaxel, Xtandi, and Xofigo® (radium Ra 223 dichloride injection, for intravenous use) [for symptomatic bone metastases] are all category 1 recommended options.
  - If there are visceral metastases, and if it is adenocarcinoma (majority), Xtandi and docetaxel are category 1 recommended options. Zytiga and prednisone, mitoxantrone with prednisone, or other secondary hormone therapies are other options (all category 2A).
  - For no visceral metastases, if patients had received prior therapy with Xtandi or Zytiga, then docetaxel and Xofigo are the category 1 options for subsequent therapy. If patients received prior docetaxel

therapy, then Xtandi, Zytiga, Xofigo, and cabazitaxel are the category 1 options. For subsequent therapy with visceral metastases, docetaxel is the recommended category 1 option, if either Xtandi or Zytiga were used as prior therapies. For prior therapy with docetaxel, Xtandi, Zytiga, cabazitaxel are the recommended category 1 options.

- For metastatic, castration-naïve disease, ADT in combination with abirateron + prednisone, Erleada, and Xtandi are all category 1 recommended options. Yonsa (abiraterone acetate) with methylprednisolone is a category 2B recommendation.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Xtandi. All approvals are provided for 3 years in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xtandi is recommended in those who meet the following criteria:

FDA-Approved Indication

~~64.~~61. **Prostate Cancer –Castration-Resistant (CRPC) [Metastatic or Non-Metastatic].** Approve for 3 years if the patient meets the following criteria (A or B):

A) The medication is used concurrently with a gonadotropin-releasing hormone (GnRH) analog.
Note: Examples are Lupron (leuprolide for injection), Lupron Depot (leuprolide acetate for depot suspension), Trelstar (triptorelin pamoate for injectable suspension), Zoladex (goserelin acetate implant), Vantas (histrelin acetate subcutaneous implant), Firmagon (degarelix for injection); OR

B) The patient has had a bilateral orchiectomy.

2. **Prostate Cancer – Metastatic, Castration-Sensitive.** Approve for 3 years if the patient meets one of the following criteria (A or B):

A) The medication is used concurrently with a gonadotropin-releasing hormone (GnRH) analog.
Note: Examples are Lupron (leuprolide for injection), Lupron Depot (leuprolide acetate for depot suspension), Trelstar (triptorelin pamoate for injectable suspension), Zoladex (goserelin acetate implant), Vantas (histrelin acetate subcutaneous implant), Firmagon (degarelix for injection); OR

B) The patient has had a bilateral orchiectomy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Xtandi has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

265. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

407. Xtandi® [prescribing information]. Northbrook, IL: Astellas Pharma US, Inc.; December 2019.
2. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (Version 4.2019 – August 19, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed February 25, 2020.

HISTORY

Type of Revision	Summary of Changes*	Date Reviewed
Early Annual revision	No criteria changes	02/01/2017
Annual revision	No criteria changes	02/28/2018
Selected revision	Xtandi is now FDA-approved for use in CRPC, regardless of metastatic status. Modified approval condition to match FDA indication. Deleted separate approval for non-metastatic CRPC from Other Uses with Supportive Evidence.	07/25/2018
Annual revision	No criteria changes	02/27/2019
Selected revision	For all indications, added criteria for concomitant use of Xtandi with GnRH agonist or patient has had bilateral orchiectomy, as per Xtandi dosing requirements. Based on Phase III Enzamet trial and guideline support, added approval indication for Xtandi use in metastatic castration-sensitive prostate cancer under "Other Uses with Supportive Evidence."	10/09/2019
Update	01/03/2020. Deleted "Other Uses with Supportive Evidence" heading since metastatic castration-sensitive prostate cancer is now an FDA-approved use for Xtandi.	N/A
Annual revision	For concurrent use of Xtandi with gonadotropin-releasing hormone "agonist", changed criteria to state "analog" since both agonists and antagonist can be used. Added Firmagon as an example for antagonist.	03/04/2020

N/A – Not applicable.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Yonsa® (abiraterone acetate tablets – Sun Pharmaceutical Industries, Inc.)

DATE REVIEWED: 06/10/2020

OVERVIEW

Yonsa is an androgen biosynthesis inhibitor that inhibits the enzyme 17 α-hydroxylase/C17,20-lyase (CYP17).[1] This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis. Yonsa, in combination with methylprednisolone, is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC). Inhibition of CYP17 by Yonsa can also result in increased mineralocorticoid production by the adrenal glands; the use of methylprednisolone with Yonsa is to counteract this mineralocorticoid excess.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on prostate cancer (version 2.2019 – April 17, 2019) have the following recommendations for Zytiga® [abiraterone acetate tablets] and Yonsa.[2]

- At initial diagnosis, for patients classified in the regional risk group (metastases in regional nodes [N1] with no distant metastases [M0]) and with a > 5 year expected patient survival, external beam radiation therapy (EBRT) + androgen deprivation therapy (ADT) [category 1] + Zytiga and prednisone (category 2A) or Yonsa and methylprednisolone (category 2B) are recommended options. ADT (without EBRT) ± Zytiga and prednisone is a category 2A recommended option in this setting; ADT + Yonsa and methylprednisolone is a category 2B recommendation.
- If patients are positive for distant metastasis (M1) and have castration-naïve disease, ADT + Zytiga and prednisone and ADT + docetaxel are both category 1 recommended options. ADT + Yonsa and methylprednisolone is a category 2B recommendation in this setting.
- For patients who progress to CRPC and are positive for distant metastasis, M1 and there are no visceral metastases, Zytiga and prednisone, docetaxel, Xtandi, and Xofigo® (radium Ra 223 dichloride injection, for intravenous use) [for symptomatic bone metastases] are all category 1 recommended options. Yonsa + methylprednisolone is a category 2A recommendation for mCRPC either as first-line or subsequent therapy option.

- If there are visceral metastases, Xtandi and docetaxel are category 1 recommended options. Zytiga and prednisone, Yonsa and methylprednisolone are category 2A recommendations for first-line or second-line treatment after Xtandi. If docetaxel was used previously, Zytiga and prednisone is a category 1 recommendation; Yonsa and methylprednisolone is a category 2A recommendation.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Yonsa. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Yonsa is recommended in those who meet the following criteria:

FDA-Approved Indication

4. Prostate Cancer – Metastatic, Castration-Resistant (mCRPC). Approve for 3 years if the patient meets the following criteria (A and B):
- **A)** The medication is used in combination with methylprednisolone; AND
- **B)** The patient meets ONE of the following criteria (i or ii):
  - **i.** The medication is concurrently used with a gonadotropin-releasing hormone (GnRH) analog. Note: Examples are Lupron (leuprolide for injection), Lupron Depot (leuprolide acetate for depot suspension), Trelstar (triptorelin pamoate for injectable suspension), Zoladex (goserelin acetate implant), Vantas (histrelin acetate subcutaneous implant), Firmagon (degarelix for injection); OR
  - **ii.** The patient has had a bilateral orchiectomy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Yonsa has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

266. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

58. Yonsa® tablets [prescribing information]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; May 2018.
59. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (Version 2. 2020 – May 21, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed June 8, 2020.

HISTORY

Type of Revision	Summary of Changes*	Date Reviewed
New Policy	New criteria	05/23/2018
Annual revision	No criteria changes	05/22/2019
Annual revision	Added requirement of gonadotropin releasing-hormone analog for use with Yonsa or bilateral orchiectomy.	06/10/2020

POLICY: Oncology – Zejula Prior Authorization Policy
- Zejula™ (niraparib capsules – Tesaro, Inc.)

REVIEW DATE: 12/09/2020

OVERVIEW

Zejula, a poly (ADP-ribose) polymerase (PARP) inhibitor, is indicated:[1]

- **Ovarian, fallopian tube, primary peritoneal cancer**, **maintenance treatment** of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.
- **Ovarian, fallopian tube, primary peritoneal cancer**, **maintenance treatment** of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.
- **Ovarian, fallopian tube, primary peritoneal cancer**, **treatment** of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with three or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either: a) a deleterious or suspected deleterious BRCA mutation OR b) genomic instability and who have progressed more than six months after response to the last platinum-based chemotherapy.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for ovarian cancer (version 1.2020 – March 11, 2020) has the following recommendations:[2]

Recurrent Disease – Treatment

For recurrent disease, Lynparza™ (olaparib capsules), Rubraca™ (rucaparib tablets), and Zejula are among the preferred targeted therapy agents for both platinum-sensitive and platinum-resistant disease (all category 2A). All are recommended following two or more lines of chemotherapy (Lynparza and Rubraca) or three or more lines of chemotherapy (Zejula) are otherwise recommended as per their FDA-approved use in the treatment of patients with advanced ovarian cancer. Zejula + bevacizumab (category 2A) is also an Other Recommended targeted therapy regimen for platinum-sensitive disease. NCCN lists several other potentially active agents for recurrence therapy.

First-Line Maintenance

Maintenance recommendations following primary treatment (first-line maintenance) apply to stage II, III, or IV ovarian cancer after primary treatment if the patient is in complete or partial remission. In patients with a germline or somatic *BRCA* mutation, both Lynparza and Zejula have a category 1 recommendation if no bevacizumab was used during primary therapy. If bevacizumab was used during primary therapy for patients with a germline or somatic *BRCA* mutation, Lynparza + bevacizumab is a category 1 recommendation for maintenance, whereas monotherapy with Lynparza or Zejula have category 2A recommendations. For patients with *BRCA* wild-type or unknown mutation status, Zejula (if no bevacizumab during primary therapy) and Lynparza + bevacizumab (if bevacizumab was used during primary therapy) are among the recommendations for maintenance (category 2A for both).

Recurrent Disease – Maintenance

In patients with platinum-sensitive disease who have completed at least two lines of platinum-based therapy for persistent disease or recurrence and have achieved a complete or partial response, Zejula, Rubraca, or Lynparza (all category 2A) can be considered for maintenance therapy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zejula. All approvals are provided for 3 years in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zejula is recommended in those who meet the following criteria:

FDA-Approved Indications

~~65.~~62. **Ovarian, Fallopian Tube, or Primary Peritoneal Cancer – Maintenance Therapy.** Approve for 3 years if the patient meets the following (A, and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient is in complete or partial response after platinum-based chemotherapy regimen.
  Note: Examples of chemotherapy regimens are carboplatin with gemcitabine, carboplatin with paclitaxel, cisplatin with gemcitabine.

2. **Ovarian, Fallopian Tube, or Primary Peritoneal Cancer – Treatment.** Approve for 3 years if the patient meets the following criteria (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has tried at least three prior chemotherapy regimens; AND
     Note: Examples of chemotherapy regimens are carboplatin/gemcitabine, carboplatin/liposomal doxorubicin, carboplatin/paclitaxel, cisplatin/gemcitabine, capecitabine, irinotecan.
   - **C)** Patient has homologous recombination deficiency (HRD)-positive disease as confirmed by an approved test.
     Note: HRD-positive disease includes patients with *BRCA* mutation-positive disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zejula is not recommended in the following situations:

267. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

334. Zejula™ capsules [prescribing information]. Waltham, MA: Tesaro, Inc.; April 2020.
335. The NCCN Ovarian Cancer Clinical Practice Guidelines in Oncology (version 1.2020 – March 11, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 7, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	04/19/2017
Early Annual Revision	Deleted criteria requiring at least two prior chemotherapy regimens to align it with FDA approved indication. Added qualifier "Maintenance Therapy" to approval condition description.	02/07/2018
Annual Revision	Modified Maintenance Therapy criteria in recurrent disease setting to state that it is after at least two lines of platinum-based chemotherapy, based on guidelines.	02/06/2019
Early Annual Revision	Added new indication for Zejula use in treatment setting.	11/20/2019
Selected Revision	In "Maintenance Therapy" indication, deleted criteria "patient has recurrent disease."	03/11/2020
Selected Revision	Due to the FDA approval of Zejula in the maintenance therapy setting after first-line chemotherapy, deleted reference to "at least two" platinum-based chemotherapies.	05/13/2020
Annual Revision	**Ovarian, Fallopian Tube, or Primary Peritoneal Cancer**: Added age criteria for both indications (Maintenance and Treatment).	12/09/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Zelboraf Prior Authorization Policy

- Zelboraf® (vemurafenib tablets – Genentech/Daiichi Sankyo)

REVIEW DATE: 07/15/2020

OVERVIEW

Zelboraf, a BRAF inhibitor, is indicated for the following indications:[1]

- **Erdheim-Chester disease**, for treatment of patients with the *BRAF V600* mutation.
- **Melanoma**, for treatment of unresectable or metastatic disease with *BRAF V600E* mutation as detected by an FDA-approved test.

Of note, Cotellic® (cobimetinib tablets) is a MEK inhibitor that is indicated to be given in combination with Zelboraf in a similar patient population with melanoma). Zelboraf is not recommended for use in patients with wild-type BRAF melanoma.

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines support use of Zelboraf in multiple cancers.

- **Melanoma:** Guidelines (version 3.2020 – May 18, 2020) recommend BRAF/MEK inhibitor combinations for first-line (preferred if clinically needed for early response) and subsequent treatment of metastatic or unresectable melanoma with a *V600* activating mutation.[2] While combination BRAF/MEK inhibition is preferred, if a combination is contraindicated, monotherapy with a BRAF inhibitor (Tafinlar® [dabrafenib capsules] or Zelboraf) is a recommended option, particularly if the patient is not a candidate for checkpoint immunotherapy. Following resection of limited metastatic disease with a *BRAF V600*-activating mutation, BRAF/MEK combination therapy is among the treatment options for patients with no evidence of disease. Tafinlar + Mekinist® (trametinib tablets) is also recommended in guidelines as adjuvant therapy (including for nodal recurrence) in some patients with Stage III disease, including use post-surgery or use after complete lymph node dissection. If unacceptable toxicity to Tafinlar/Mekinist, other BRAF/MEK combinations can be considered.
- **Hairy Cell Leukemia:** NCCN guidelines for hairy cell leukemia (version 1.2020 – August 23, 2019) list Zelboraf ± rituximab among the treatment options for relapsed or refractory disease.[3]

- **Non-Small Cell Lung Cancer:** NCCN guidelines (version 6.2020 – June 25, 2020) list Tafinlar + Mekinist among the first-line therapy and subsequent therapy options for tumors with a *BRAF* mutation.[4] NCCN also notes that monotherapy with a BRAF inhibitor (Tafinlar or Zelboraf) is a treatment option when combination therapy is not tolerated.
- **Thyroid Cancer:** Guidelines (version 1.2020 – June 12, 2020) list Tafinlar + Mekinist as a treatment option for metastatic anaplastic thyroid cancer with a *BRAF* mutation.[5] Tafinlar and Zelboraf are also treatment options for the treatment of iodine-refractory differentiated thyroid cancer (follicular, Hürthle cell, and papillary cancer subtypes) with a *BRAF V600* mutation.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Zelboraf. All approvals are provided for 3 years unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zelboraf is recommended in those who meet the following criteria:

FDA-Approved Indications

7. **Erdheim-Chester Disease.** Approve for 3 years if the patient has *BRAF V600* mutation-positive disease.

8. **Melanoma.** Approve Zelboraf for 3 years if the patient meets BOTH of the following (A and B):
   A) Patient has unresectable, advanced, or metastatic melanoma; AND
   B) Patient has *BRAF V600* mutation-positive disease.

Other Uses with Supportive Evidence

9. **Hairy Cell Leukemia.** Approve for 3 years if the patient has tried at least one other systemic therapy for hairy cell leukemia.
   Note: Examples of other systemic therapies include cladribine, Nipent (pentostatin injection), rituximab injection, Intron A (interferon alpha-2b injection).

10. **Non-Small Cell Lung Cancer.** Approve for 3 years if the patient has *BRAF V600E* mutation-positive disease.

11. **Thyroid Cancer, Differentiated.** Approve Zelboraf for 3 years if the patient meets ALL of the following conditions (A, B, and C):
    D) Patient has differentiated thyroid carcinoma; AND
    Note: Examples of differentiated thyroid carcinoma include papillary, follicular, or Hürthle cell thyroid cancers.
    E) Patient has disease that is refractory to radioactive iodine therapy; AND
    F) Patient has *BRAF* mutation-positive disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zelboraf is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

408. Zelboraf® tablet, oral [prescribing information]. South San Francisco, CA: Genentech USA, Inc.; May 2020.
409. The NCCN Melanoma Clinical Practice Guidelines in Oncology (Version 3.2020 – May 18, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 2, 2020.
410. The NCCN Hairy Cell Leukemia Clinical Practice Guidelines in Oncology (Version 1.2020 – August 23, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 2, 2020.
411. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 6.2020 – June 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 2, 2020.
412. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (Version 1.2020 – June 12, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 2, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early annual revision	Align criteria for melanoma with Tafinlar PA criteria; remove criteria that does not allow coverage in patients who had disease progression while on a BRAF inhibitor. Remove continuation criteria in melanoma; now all approvals require that the patient has unresectable, advanced, or metastatic melanoma with a BRAF mutation.	05/23/2018
Annual revision	**Colon or Rectal Cancer:** Add criteria as supported by NCCN colon cancer guidelines. Criteria approve if the patient has *BRAF V600E* mutation-positive disease, and if the patient has previously used chemotherapy (including as adjuvant use), and if the agent will be used as part of a combination regimen for colon or rectal cancer. **Hairy Cell Leukemia:** To align with updated guidelines, change criteria to require at least one previous therapy (previously required two therapies prior to Zelboraf). **NSCLC:** The diagnosis was changed to remove the BRAF mutation from the approval condition. The requirement that the patient has BRAF V600E mutation was added to the criteria for patients with NSCLC.	06/18/2019
Annual revision	**Colon or Rectal Cancer:** This indication was removed from the policy. Zelboraf is no longer a recommended therapy in guidelines for colon and rectal cancer. **Hairy Cell Leukemia:** For the criterion that requires a previous therapy, clarify that that this must be a systemic therapy. Since a previous systemic therapy is required, remove the requirement that the patient has relapsed/refractory disease (not needed). Examples of systemic therapies were moved to a Note (previously listed as examples within the criteria). **Thyroid Cancer:** Examples of differentiated thyroid cancer were moved to a note (previously listed as an i.e. within criteria).	07/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Zolinza Prior Authorization Policy

- Zolinza® (vorinostat capsules – Merck)

REVIEW DATE: 07/22/2020

OVERVIEW

Zolinza, a histone deacetylase inhibitor, is indicated for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma who have progressive, persistent or recurrent disease on or following two systemic therapies.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for primary cutaneous lymphomas (Version 2.2020 – April 10, 2020) list Zolinza as a preferred systemic therapy for mycosis fungoides/Sezary syndrome.[2,3] Zolinza can be used for primary treatment or for relapsed, persistent, or refractory disease.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Zolinza. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zolinza is recommended in those who meet the following criteria:

FDA-Approved Indications

150. Cutaneous T-Cell Lymphoma including Mycosis Fungoides/Sezary Syndrome. Approve for 3 years.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zolinza is not recommended in the following situations:

160. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

506. Zolinza® capsules [prescribing information]. Whitehouse Station, NJ: Merck & Co.; December 2018.
507. The NCCN Primary Cutaneous Lymphomas Clinical Practice Guidelines in Oncology (Version 2.2020 – April 10, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed July 15, 2020.
508. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on Jul 15, 2020. Search term: vorinostat.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/24/2019
Annual revision	No criteria changes.	07/22/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Zydelig Prior Authorization Policy
- Zydelig® (idelalisib tablets – Gilead)

REVIEW DATE: 06/03/2020

OVERVIEW

Zydelig, an inhibitor of phosphatidylinositol 3-kinase, is indicated for the treatment of patients with 1) relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other comorbidities; 2) relapsed follicular B-cell non-Hodgkin lymphoma in patients who have received at least two prior systemic therapies; and 3) relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies.[1] Accelerated approval was given for the relapsed follicular B-cell non-Hodgkin lymphoma and SLL indications based on overall response rate (ORR). Improvement in patient survival or disease-related symptoms has not been established. A limitation of use for all three indications is that Zydelig is not indicated and is not recommended for first-line treatment.

Disease Overview

CLL is one of the most prevalent adult leukemias in the Western world.[5] In 2019, an estimated 20,720 patients will be diagnosed with CLL in the US, and approximately 3,930 patients will die from the disease. The condition usually is diagnosed in older adults (≥ 70 years of age) and occurs more frequently in men. The leukemic cells appear as small, mature lymphocytes. CLL and SLL are different manifestations of the same condition and are managed similarly. In CLL, many of the abnormal lymphocytes are found in the blood, as well as in the bone marrow and lymphoid tissue. In SLL, there are few, if any, abnormal lymphocytes circulating in blood and most of the disease is in the lymph nodes, bone marrow, and other lymphoid tissue. The diagnosis requires the presence of at least 5×10^9/L monoclonal B-lymphocytes in the peripheral blood. SLL requires the presence of lymphadenopathy and/or splenomegaly with $< 5 \times 10^9$/L B-lymphocytes found in the peripheral blood.

Follicular lymphoma is the most common subtype of indolent non-Hodgkin's lymphoma accounts for approximately 22% of all newly diagnosed cases of non-Hodgkin lymphoma.[8] Most cases (90%) of follicular lymphoma have a t(14;18) translocation, which results in the deregulated expression of BCL-2 protein. Pediatric type follicular lymphoma may occur, albeit rare.[8] Many patients with follicular lymphoma present with asymptomatic lymphadenopathy and bone marrow involvement is present. Some patients also have increased serum lactate dehydrogenase (LDH) is present. Patients with early stage disease generally receive radiation therapy as good responses have been achieved. Although further study is required, chemoimmunotherapy or systemic therapy plus radiation therapy may improve outcomes. Most patients present with advanced disease at diagnoses. Patients who are asymptomatic may not require immediate treatment. Rituximab, used with or without other therapies, has dramatically changed the course of treating follicular lymphoma, with noted improvement in survival. Autologous or allogeneic stem cell transplantations may be considered in some clinical scenarios but are generally reserved for patients with relapsed or refractory disease.

Guidelines

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for CLL/SLL (version 4.2020 – December 20, 2019) address CLL. Zydelig is recommended with or without rituximab for relapsed or refractory therapy for CLL in various scenarios.[5] Many other agents have a more prominent role in the first-line management of CLL.[5,6] The guidelines note that CLL and SLL are different manifestations of the same condition and are treated similarly.

The NCCN clinical practice guidelines for B-cell Lymphomas (version 1.2020 – January 22, 2020) recommend Zydelig as second-line and subsequent therapy in patients with follicular lymphoma (grade 1-2) among patients refractory to two prior therapies.[8]

The NCCN clinical practice guidelines for B-Cell Lymphomas (version 1.2020 – January 22, 2020) recommend Zydelig as second-line and subsequent therapy for marginal zone lymphomas that are relapsed/refractory to two prior therapies.[8] Other regimens are recommended first line that are primarily rituximab-based.

Safety

Zydelig has a Boxed Warning regarding fatal and serious toxicities such as hepatotoxicity, fatal and/or serious and severe diarrhea or colitis, fatal and serious pneumonitis, fatal and/or serious infections, and fatal and serious intestinal perforation.[1] Zydelig was approved with a Risk Evaluation and Mitigation Strategy (REMS) program to highlight toxicities noted in the Boxed Warning.[2] The REMS program involves a communication plan. In March 2016, the FDA issued a healthcare professionals alert regarding studies with Zydelig which revealed an increased rate of adverse events (AEs), including deaths, in clinical trials when Zydelig was used in combination with other cancer medications.[3] The manufacturer is halting six clinical trials in patients with CLL, SLL and indolent non-Hodgkin lymphomas.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Zydelig. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zydelig is recommended in those who meet the following criteria:

FDA-Approved Indications

~~66.~~63. **Chronic Lymphocytic Leukemia (CLL).** Approve for 3 years if the patient has tried at least two prior therapies.
Note: Examples include Imbruvica® (ibrutinib capsules and tablets); chlorambucil plus Gazyva® (obinutuzumab injection for intravenous use); chlorambucil plus rituximab; FCR (fludarabine, cyclophosphamide and rituximab); FR (fludarabine plus rituximab); PCR (pentostatin, cyclophosphamide, rituximab); Treanda® (bendamustine injection) with or without rituximab; high-dose methylprednisolone (HDMP) plus rituximab; Campath® (alemtuzumab injection for intravenous use) with or without rituximab; Venclexta® (venetoclax tablets) with or without rituximab; Calquence® (acalabrutinib capsules); Gazyva; rituximab; Arzerra® (ofatumumab injection for intravenous use); chlorambucil; Venclexta plus Gazyva; or Copiktra (duvelisib capsules).

~~67.~~64. **Follicular Lymphoma.** Approve for 3 years if the patient has tried at least two prior therapies.
Note: Examples include Treanda® (bendamustine injection) plus rituximab; Treanda plus Gazyva®

(obinutuzumab injection for intravenous use); CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) plus Gazyyva or rituximab; CVP (cyclophosphamide, vincristine, prednisone) plus Gazyva or rituximab; chlorambucil with or without rituximab; cyclophosphamide with or without rituximab; Gazyva; Revlimid® (lenalidomide capsules); Copiktra™ (duvelisib capsules); or Aliqopa® (copanlisib injection for intravenous use).

~~68.~~65. **Small Lymphocytic Lymphoma (SLL).** Approve for 3 years if the patient has tried at least two prior therapies.
Note: Examples include Imbruvica® (ibrutinib capsules or tablets); chlorambucil plus Gazyva® (obinutuzumab injection for intravenous use); chlorambucil plus rituximab; FCR (fludarabine, cyclophosphamide and rituximab); FR (fludarabine plus rituximab); PCR (pentostatin, cyclophosphamide, rituximab); Treanda® (bendamustine injection) with or without rituximab; high-dose methylprednisolone (HDMP) plus rituximab; Venclexta® (venetoclax tablets) with or without rituximab; Calquence® (acalabrutinib capsules); Gazyva; rituximab; Arzerra® (ofatumumab injection for intravenous use); chlorambucil; Venclexta plus Gazyva; or Copiktra (duvelisib capsules).

Other Uses with Supportive Evidence

268. Marginal Zone Lymphoma. Approve for 3 years if the patient has tried at least two other therapies.
Note: Examples include rituximab; Treanda® (bendamustine injection for intravenous use) plus rituximab; RCHOP (rituximab, cyclophosphamide, vincristine, prednisone); RCVP (rituximab, cyclophosphamide, vincristine, prednisone); chlorambucil with or without rituximab; cyclophosphamide with or without rituximab; Imbruvica® (ibrutinib tablets and capsules); Copiktra™ (duvelisib capsules); Revlimid® (lenalidomide capsules) with or without rituximab; or Aliqopa® (copanlisib injection for intravenous use).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Zydelig has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

413. Zydelig® tablets [prescribing information]. Foster City, CA: Gilead Sciences; October 2018.
414. Zydelig REMS program. Available at: http://www.zydeligrems.com/. Accessed on May 29, 2020.
415. U.S. Food and Drug Administration. FDA alerts healthcare professionals about clinical trials with Zydelig (idelalisib) in combination with other cancer medicines. Date: 03/14/2016. Available at: http://www.fda.gov/drugs/drugsafety/ucm490618.htm. Accessed on May 29, 2020.
416. Furman RR, Sharman JP, Coutry SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2014;370(11):997-1007.
417. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (Version 1.2020 – January 22, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 29, 2020.
418. Hallek M, Shanafelt TD, Eichhorst B. Chronic lymphocytic leukemia. *Lancet*. 2018;391:1524-1537.
419. Gopal AK, Kahl BS, de Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med*. 2014;370(11):1008-1018.
420. The NCCN B-cell Lymphomas Clinical Practice Guidelines in Oncology (Version 1.2020 – January 22, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 29, 2020.

421. Salles G, Schuster SJ, de Vos S, et al. Efficacy and safety of idelalisib in patients with relapsed, rituximab- and alkylating agent-refractory follicular lymphoma: a subgroup analysis of a phase 2 study. *Haematologica*. 2017;102(4):e156-e159.
422. Gopal AK, Kahl BS, Flowers CR, et al. Idelalisib is effective in patients with high-risk follicular lymphoma and early relapse after initial chemoimmunotherapy. *Blood*. 2017;129(22):3037-3039.

HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	Alternatives for CLL revised (agents removed or added) based on NCCN guidelines. For Follicular B-Cell Non-Hodgkin Lymphoma changed the requirement that patients have tried two prior therapies instead of one therapy, to make it in-line with FDA-approved labeling; therapy alternatives were slightly revised based on NCCN guidelines. For SLL changed the requirement that patients have tried two prior therapies instead of one therapy to make it in-line with FDA-approved labeling; therapy alternatives were slightly revised based on NCCN guidelines. Criteria added regarding approval for marginal zone lymphoma if the patient had tried two other prior therapies based on NCCN guidelines.	05/16/2018
Annual Revision	For clarity, the reference to Rituxan when listing previous required therapies was changed to "rituximab". The following changes were also made: 1. **Chronic Lymphocytic Leukemia:** The number of therapies required prior to approval of Zydelig was changed from one to two. Also, Venclexta plus Gazyva and Copiktra were added to the list of examples of agents that count toward this requirement. 2. **Follicular Lymphoma:** The wording "B-Cell Non-Hodgkin" was removed from the cited condition. The RCHOP regimen was removed from the listing of alternatives and the regimen that cited "CHOP plus Gazyva" was the changed to "CHOP plus Gazyva or rituximab". Likewise, the RCVP alternative was changed to state "CVP plus Gazyva or rituximab". Copiktra was also listed as an alternative that counts as the requirement to try two prior therapies. 3. **Small Lymphocytic Lymphoma:** Venclexta plus Gazyva and Copiktra were added to the list of examples of agents that count toward the requirement of a trial of two prior therapies. 4. **Marginal Zone Lymphoma:** Copiktra and Revlimid (with or without rituximab) were added as alternatives that count towards the requirement of two prior therapies.	06/05/2019
Annual Revision	**The following changes were made:** 1. **Chronic Lymphocytic Leukemia:** The wording of "at least" was added to the requirement that patients try two therapies. Also, the examples of therapies were removed from the criteria and placed into a note. Chlorambucil plus Arzerra® (ofatumumab injection for intravenous use) was removed from the list of examples. 2. **Follicular Lymphoma:** The wording of "at least" was added to the requirement that patients try two therapies. Also, the examples of therapies were removed from the criteria and placed into a note. 3. **Small Lymphocytic Lymphoma:** The wording of "at least" was added to the requirement that patients try two therapies. Also, the examples of therapies were removed from the criteria and placed into a note. Chlorambucil plus Arzerra® (ofatumumab injection for intravenous use) was removed from the list of examples. 4. **Marginal Zone Lymphoma:** The wording of "at least" was added to the requirement that patients try two therapies. Also, the examples of therapies were removed from the criteria and placed into a note.	06/03/2020

CLL – Chronic lymphocytic leukemia; NCCN – National Comprehensive Cancer Network; FDA – Food and Drug Administration; SLL – Small lymphocytic lymphoma.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Zykadia™ (ceritinib capsules and tablets – Novartis Pharmaceuticals)

DATE REVIEWED: 06/10/2020

OVERVIEW

Zykadia, a kinase inhibitor, is indicated for the treatment of patients with anaplastic lymphoma kinase (*ALK*)-positive metastatic non-small cell lung cancer (NSCLC), as detected by an FDA-approved test.[1] Using biochemical or cellular assays at clinically relevant concentrations, it has been noted that Zykadia inhibits *ALK*, insulin-like growth factor 1 receptor (IGF-1R), insulin receptor (InsR), and c-ros oncogene 1 (ROS1). Among these, Zykadia is most effective against *ALK*.

A multicenter, open-label, Phase II study evaluated the efficacy of Zykadia in patients with ROS1-rearranged NSCLC (n = 32).[5] All patients, except two, were Xalkori treatment-naïve. Patients received Zykadia at the recommended dose of 750 mg/day. The overall objective response rate (ORR) was 62% (95% CI: 45%, 77%); in Xalkori-naïve patients the ORR was 67%. The median PFS was 9.3 months and the median PFS for Xalkori-naïve patients was 19.3 months (95% CI: 1, 37). The median OS was 24 months (95% CI: 5, 43) with a 6-month OS rate of 84% and a 12-month OS rate of 56%. Only eight patients had brain metastases at baseline. The overall intracranial ORR was 25% (n = 2/8) and the DCR was 63% (n = 5/8). The NCCN NSCLC guidelines recommend Xalkori (preferred) or Zykadia as first-line options for ROS1-positive NSCLC (both category 2A).

GUIDELINES

According to the National Comprehensive Cancer Network (NCCN) NSCLC guidelines (version 5.2020 – May 27, 2020), Alecensa® (alectinib capsules) is the "preferred" first-line therapy for ALK-positive NSCLC. Zykadia and Alunbrig® (brigatinib tablets) are "Other Recommended" first-line therapies. Xalkori® (crizotinib capsules) is a category 1 agent under "Useful in Certain Circumstances". and [[2] For progression on Alecensa, Alunbrig, or Zykadia, for multiple systemic lesions, Lorbrena (lorlatinib tablets) is a recommended option or initial systemic therapy options can be considered (both category 2A). Xalkori (preferred) or Zykadia are recommended as first-line therapy for ROS1 rearrangement-positive NSCLC (both category 2A). Lorbrena is recommended for subsequent therapy.

The NCCN guidelines for soft tissue sarcoma (version 2.2019 – February 4, 2019) recommend Zykadia as a single-agent therapy for the treatment of IMT with ALK translocation (category 2A recommendation).[4-5]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Zykadia. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zykadia is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Non-Small Cell Lung Cancer (NSCLC).** Approve for 3 years if the patient has metastatic anaplastic lymphoma kinase (*ALK*)-positive NSCLC as detected by an approved test.

Other Uses with Supportive Evidence

2. **Non-Small Cell Lung Cancer (NSCLC) with ROS1 Rearrangement – First-Line Therapy.** Approve for 3 years.

3. **Soft Tissue Sarcoma Inflammatory Myofibroblastic Tumor (IMT) with ALK Translocation.** Approve for 3 years.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Zykadia has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

269. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

423. Zykadia™ capsules and tablets [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals; March 2019.
424. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 5.2020 – May 27, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 8, 2020.
425. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (version 2.2019 – February 4, 2019). ©2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 20, 2019.
426. The NCCN Drugs & Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 8, 2020. Search terms: ceritinib.
427. Lim SM, Kim HR, Lee JS, et al. Open-label, multicenter, Phase II study of ceritinib in patients with non-small cell lung cancer harboring ROS1 rearrangement. *J Clin Oncol*. 2017;35:2613-2618.

History

Type of Revision	Summary of Changes*	Date Reviewed
Annual revision	No criteria changes	06/17/2015
Annual revision	Added new approval criteria under Other Uses with Supportive Evidence in patients with soft tissue sarcoma inflammatory myofibroblastic tumor with ALK translocation based on NCCN soft tissue sarcoma guidelines.	07/13/2016
Selected revision	Added new approval criteria under Other Uses with Supportive Evidence for Zykadia use in the first-line setting. Deleted Non-Small Cell Lung Cancer ALK-positive, Xalkori treatment-naïve from Conditions Not Recommended for Approval.	04/05/2017
Early annual revision	Zykadia has FDA approval in first-line use. Deleted all criteria for "After Xalkori Therapy". Also deleted wording "First-Line Therapy" since it's not needed.	06/07/2017
Selected revision	Added approval criteria for ROS1 positive non-small cell lung cancer based on guideline recommendations under Other Uses with Supportive Evidence. Deleted NSCLC - ALK status is negative or unknown from Conditions Not Recommended for Approval since patients without ALK positive or ROS1 testing would not get approval anyways based on current criteria.	01/17/2018
Annual revision	No criteria changes	05/23/2018
Annual revision	No criteria changes. Tablet formulation also available.	05/22/2019
Annual revision	No criteria changes	06/10/2020

ALK – Anaplastic lymphoma kinase; NCCN – National Comprehensive Cancer Network; NSCLC – Non-small cell lung cancer

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Adcetris Prior Authorization Policy

- Adcetris® (brentuximab injection for intravenous use – Seattle Genetics, Inc.)

REVIEW DATE: 09/23/2020

OVERVIEW

Adcetris, a CD30 directed antibody conjugate, is indicated for the following uses:

- **Classical Hodgkin lymphoma**, in patients with previously untreated Stage III or IV disease, in combination with doxorubicin, vinblastine, and dacarbazine.
- **Classical Hodgkin lymphoma**, in patients at high risk of relapse or progression as post-autologous hematopoietic stem cell transplantation consolidation.
- **Classical Hodgkin lymphoma**, in patients who are not autologous hematopoietic stem cell transplantation candidates and after failure of autologous hematopoietic stem cell transplantation or after failure of at least two prior multi-agent chemotherapy regimens.
- **Primary cutaneous anaplastic large cell lymphoma** or **CD30-expressing mycosis fungoides**, in patients who have received prior systemic therapy.
- **Systemic anaplastic large cell lymphoma** or other **CD30-expressing peripheral T-cell lymphomas**, including angioimmunoblastic T-cell lymphoma and peripheral T-cell lymphomas not otherwise specified, in previously untreated patients in combination with cyclophosphamide, doxorubicin, and prednisone.
- **Systemic anaplastic large cell lymphoma**, in patients who have failed at least one prior multi-agent chemotherapy regimen.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) Hodgkin Lymphoma Clinical Practice Guidelines (version 2.2020 – April 17, 2020) recommend Adcetris for the treatment of classical Hodgkin Lymphoma in combination with chemotherapy, as second-line or subsequent therapy for relapsed or refractory disease, as maintenance therapy following high-dose therapy and autologous stem cell rescue for relapsed or refractory disease, or as palliative therapy.[2,3]

The NCCN T-Cell Lymphomas Clinical Practice Guidelines (version 1.2020 – January 6, 2020) recommend Adcetris as a preferred first-line therapy in combination with CHP (cyclophosphamide, doxorubicin, prednisone) for the treatment of CD30+ anaplastic large cell lymphoma (ALCL), CD30+ peripheral T-cell lymphoma not otherwise specified, CD30+ angioimmunoblastic T-cell lymphoma, CD30+ enteropathy-associated T-cell lymphoma, CD30+ monomorphic epitheliotropic intestinal T-cell lymphoma, CD30+ nodal peripheral T-cell lymphoma with T follicular helper (TFH) phenotype, CD30+ hepatosplenic gamma-delta T-cell lymphoma, or CD30+ follicular T-cell lymphoma.[2,4] As a single agent for subsequent therapy for relapsed/refractory ALCL, CD30+ peripheral T-cell lymphoma, CD30+ hepatosplenic gamma-delta T-cell lymphoma, CD30+ extranodal NK/T-cell lymphoma – nasal type, or CD30+ angioimmunoblastic T-cell lymphoma. As a single agent or as a component of CHP for the treatment of CD30+ adult T-cell leukemia/lymphoma. As a single agent or in combination with CHP for the adjuvant treatment of CD30+ breast implant-associated ALCL.

The NCCN Primary Cutaneous Lymphomas Clinical Practices Guidelines (version 2.2020 – April 10, 2020) recommend Adcetris for the systemic therapy of CD30+: mycosis fungoides/Sezary syndrome, primary cutaneous anaplastic large cell lymphoma, and lymphomatoid papulosis.[2,5]

The NCCN B-Cell Lymphomas Clinical Practice Guidelines (version 4.2020 – August 13, 2020) recommend Adcetris for the second-line or subsequent treatment of histologic transformation of follicular lymphoma to CD30+ diffuse large B-cell lymphoma (DLBCL), histologic transformation of nodal marginal zone lymphoma to CD30+ DLBCL, CD30+ DLBCL, CD30+ high-grade B-cell lymphoma, CD30+ acquired immunodeficiency syndrome (AIDS)-related B-cell lymphoma, and CD30+ post-transplant lymphoproliferative disorders.[2,6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Adcetris. All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Adcetris as well as the monitoring required for adverse events and long-term efficacy, approval requires Adcetris to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Adcetris is recommended in those who meet the following criteria:

FDA-Approved Indications

151. Hodgkin Lymphoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has classical Hodgkin lymphoma; AND
- **C)** The medication is prescribed by or in consultation with an oncologist.

152. T-Cell Lymphoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Adcetris is used for CD30+ T-cell lymphoma; AND
  Note: Examples include CD30+ systemic anaplastic large cell lymphoma, CD30+ angioimmunoblastic T-cell lymphoma, CD30+ peripheral T-cell lymphoma not otherwise specified, CD30+ mycosis fungoides/Sezary syndrome, CD30+ primary cutaneous anaplastic large cell lymphoma, CD30+ lymphomatoid papulosis, CD30+ breast implant-associated anaplastic large cell lymphoma, CD30+ adult T-cell leukemia/lymphoma.

C) The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

153. B-Cell Lymphoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Adcetris is used as second-line or subsequent therapy for CD30+ B-cell lymphoma; AND
  Note: Examples include CD30+ diffuse large B-cell lymphoma, CD30+ post-transplant lymphoproliferative disorders, CD30+ AIDS-related B-cell lymphoma, CD30+ high-grade B-cell lymphoma.
- **C)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Adcetris is not recommended in the following situations:

161. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

509. Adcetris® injection [prescribing information]. Bothell, WA: Seattle Genetics, Inc.; October 2019.
510. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 15, 2020. Search term: brentuximab.
511. The NCCN Hodgkin Lymphoma Clinical Practice Guidelines in Oncology (Version 2.2020 – April 17, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 15, 2020.
512. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 1.2020 – January 6, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 15, 2020.
513. The NCCN Primary Cutaneous Lymphomas Clinical Practice Guidelines in Oncology (Version 2.2020 – April 10, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 15, 2020.
514. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 4.2020 – August 13, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 15, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	09/25/2019
Annual revision	No criteria changes.	09/23/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Aliqopa Prior Authorization Policy
- Aliqopa™ (copanlisib injection for intravenous use – Bayer)

REVIEW DATE: 09/02/2020

OVERVIEW

Aliqopa, a kinase inhibitor, is indicated for the treatment of adults with relapsed follicular lymphoma who have received at least two prior systemic therapies.[1] This indication was granted accelerated approval based on overall response rate. Continued approval may be dependent on verification and description of clinical benefit in a confirmatory trial.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on B-Cell Lymphomas (version 4.2020 – August 13, 2020) recommend Aliqopa as subsequent therapy for relapsed/refractory follicular lymphoma (grade 1 or 2), gastric and nongastric MALT, splenic marginal zone lymphoma, and nodal marginal zone lymphoma after ≥ 2 prior therapies.[2,3]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Aliqopa. All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Aloqopa as well as the monitoring required for adverse events and long-term efficacy, approval requires Aliqopa to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Aliqopa is recommended in those who meet the following criteria:

FDA-Approved Indications

154. Follicular Lymphoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has received ≥ 2 prior systemic therapies; AND
  Note: Examples of systemic therapies include bendamustine, cyclophosphamide, doxorubicin, vincristine, rituximab product (e.g., Rituxan, Truxima), Gazyva® (obinutuzumab injection for intravenous use).
- **C)** Aliqopa is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

155. Marginal Zone Lymphoma (NOTE: Includes Gastric MALT, Nongastric MALT, Nodal Marginal Zone Lymphoma, and Splenic Marginal Zone Lymphoma). Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has received ≥ 2 prior systemic therapies; AND
  Note: Examples of systemic therapies include bendamustine, cyclophosphamide, doxorubicin, vincristine, rituximab product (e.g., Rituxan, Truxima), Gazyva® (obinutuzumab injection for intravenous use).
- **C)** Aliqopa is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Aliqopa is not recommended in the following situations:

162. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

515. Aliqopa™ injection for intravenous use [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; February 2020.
516. The NCCN B-Cell Lymphoma Clinical Practice Guidelines in Oncology (Version 4.2020 – August 13, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed August 24, 2020.
517. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 24, 2020. Search term: copanlisib.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	09/04/2019
Annual Revision	No criteria changes.	09/02/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Arsenic Trioxide Prior Authorization Policy

- Arsenic Trioxide injection for intravenous use (Trisenox® – Teva Pharmaceuticals, generics)

REVIEW DATE: 09/23/2020

OVERVIEW

Arsenic trioxide is indicated for **acute promyelocytic leukemia (APL)**:

- In combination with tretinoin for the treatment of adults with newly-diagnosed low-risk disease whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression.
- For induction of remission and consolidation in patients with APL who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Acute Myeloid Leukemia (version 3.2020 – December 23, 2019) recommends arsenic trioxide for induction and consolidation therapy in low-risk (white blood cell [WBC] count < 10,000/µL) and in high risk (WBC > 10,000/µL) APL with or without cardiac issues.[2,3] NCCN also recommends arsenic trioxide for the first relapse (either morphologic or molecular) and as single agent consolidation therapy in patients that are not transplant candidates and are polymerase chain reaction (PCR) negative following second remission (morphologic).

The NCCN Clinical Practice Guidelines for T-Cell Lymphoma (version 1.2020 – January 6, 2020) recommends arsenic trioxide in combination with interferon alfa-2b for the second-line or subsequent treatment of nonresponders to first-line therapy for adult T-cell leukemia/lymphoma, acute or lymphoma subtypes.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of arsenic trioxide. All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with arsenic trioxide as well as the monitoring required for adverse events and long-term efficacy, approval requires arsenic trioxide to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of arsenic trioxide is recommended in those who meet the following criteria:

FDA-Approved Indications

156. Acute Promyelocytic Leukemia. Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

157. Adult T-Cell Leukemia/Lymphoma. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):

A) Patient is ≥ 18 years of age; AND

B) Patient has acute or lymphoma subtype; AND

C) Patient has tried chemotherapy; AND
Note: Examples include CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone).

D) Arsenic trioxide will be used in combination with interferon alfa-2b; AND
Note: Includes Intron A.

E) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of arsenic trioxide is not recommended in the following situations:

163. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

518. Trisenox® injection for intravenous use [prescribing information]. North Wales, PA: Teva Pharmaceuticals; June 2019.
519. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 15, 2020. Search term: arsenic trioxide.
520. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (Version 3.2020 – December 23, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 15, 2020.
521. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 1.2020 – January 6, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://nccn.org. Accessed on September 15, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	09/25/2019
Annual Revision	No criteria changes.	09/23/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Arzerra Prior Authorization Policy

- Arzerra® (ofatumumab injection for intravenous use – Novartis)

REVIEW DATE: 10/14/2020

OVERVIEW

Arzerra is indicated for the treatment of **chronic lymphocytic leukemia** (CLL) in the following situations:

- Previously untreated patients, in combination with chlorambucil, in patients for whom fludarabine-based therapy is considered inappropriate.
- Recurrent or progressive CLL, in patients who are in complete or partial response after at least two lines of therapy.
- Refractory CLL, in patients with disease refractory to fludarabine and alemtuzumab.
- Relapsed CLL, in combination with fludarabine and cyclophosphamide.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on **B-cell lymphomas** (version 4.2020 – August 13, 2020) recommends Arzerra as a substitute for rituximab products (Rituxan, Truxima) and Gazyva (obinutuzumab injection) in patients with B-cell lymphomas experiencing rare complications such as paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis.[2,5]

The NCCN guidelines on **chronic lymphocytic leukemia/small lymphocytic lymphoma** (version 1.2021 – September 28, 2020) recommends Arzerra in combination with bendamustine for the first-line treatment of CLL/small lymphocytic lymphoma (SLL) without del(17p)/TP53 mutation; as a single agent, or in combination with fludarabine and cyclophosphamide for relapsed or refractory CLL/SLL without del(17p)/TP53 mutation; as a single agent for relapsed or refractory disease with del(17p)/TP53 mutation in patients with lymph nodes < 5 cm; and post second-line maintenance therapy following complete or partial response to treatment for relapsed or refractory disease.[2,3]

The NCCN guidelines on **Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma** (version 1.2021 – September 1, 2020) recommends Arzerra as a single agent or in combination therapy in rituximab (Rituxan, Truxima) intolerant patients, anywhere that rituximab is given, for previously treated disease that does not response to primary treatment or for relapsed or progressive disease.[2,4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Arzerra. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Arzerra as well as the monitoring required for adverse events and long-term efficacy, approval requires Arzerra to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Arzerra is recommended in those who meet the following criteria:

FDA-Approved Indications

158. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Approve for 6 months if the patient meets the following criteria (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

159. B-Cell Lymphoma. Note: Examples include follicular lymphoma, MALT lymphoma, marginal zone lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, high-grade B-cell lymphoma. Approve for 6 months if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND

B) Patient experienced an adverse event or intolerance to a rituximab product or Gazyva® (obinutuzumab injection); AND
Note: Examples of adverse events or intolerance include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, toxic epidermal necrolysis.
C) The medication is prescribed by or in consultation with an oncologist.

160. Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma. Approve for 6 months if the patient meets the following criteria (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient is intolerant to a rituximab product; AND
C) Patient has relapsed or progressive disease; AND
D) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Arzerra is not recommended in the following situations:

164. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

522. Arzerra® [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; August 2016.
523. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 1, 2020. Search term: ofatumumab.
524. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (Version 1.2021 – September 28, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 1, 2020.
525. The NCCN Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma Clinical Practice Guidelines in Oncology (Version 1.2021 – September 1, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 1, 2020.
526. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 4.2020 – August 13, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 1, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/09/2019
Annual Revision	No criteria changes.	10/14/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Asparlas Prior Authorization Policy
- Asparlas™ (calaspargase pegol mknl injection, for intravenous use)

REVIEW DATE: 12/16/2020

OVERVIEW

Asparlas is indicated as a component of a multi-agent chemotherapy regimen for the treatment of **acute lymphoblastic leukemia** (ALL) in pediatric and young adults, age 1 month to 21 years.[1]

Asparlas is a conjugate of L-asparaginase, produced by *E. coli*, and monomethoxypolyethylene glycol (mPEG) with a succinimidyl carbonate linker.[1] The succinimidyl carbonate linker forms a stable chemical

bond between mPEG and L-asparaginase. Asparlas catalyzes the conversion of L-asparagine into aspartic acid and ammonia. Leukemia cells with low expression of asparagine synthetase cannot make L-asparagine and require exogenous sources for survival. Asparlas kills leukemia cells by depleting the plasma of exogenous L-asparagine.

Guidelines

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for ALL (version 2.2020 – October 23, 2020) and pediatric ALL (version 2.2021 – October 22, 2020) state that Asparlas can be substituted for pegaspargase in patients aged 1 month to 21 years for more sustained asparaginase activity.[2-4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Asparlas. All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Asparlas as well as the monitoring required for adverse events and long-term efficacy, approval requires Asparlas to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Asparlas is recommended in those who meet the following criteria:

FDA-Approved Indications

8. Acute Lymphoblastic Leukemia. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient is 1 month to 21 years of age; AND
- **B)** Asparlas is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Asparlas is not recommended in the following situations:

165. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

527. Asparlas™ [prescribing information]. Boston, MA: Servier Pharmaceuticals LLC; June 2020.
528. The NCCN Drugs & Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 8, 2020. Search term: calaspargase.
529. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (Version 2.2020 – October 23, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 8, 2020.
530. The NCCN Pediatric Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (Version 2.2021 – October 22, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 8, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/03/2019
Annual Revision	No criteria changes.	12/11/2019
Annual Revision	No criteria changes.	12/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Azedra Prior Authorization Policy
- Azedra® (iobenguane I 131 injection, for intravenous use – Progenics Pharmaceuticals, Inc.)

REVIEW DATE: 09/02/2020

OVERVIEW

Azedra is a radioactive therapeutic agent indicated for the treatment of adult and pediatric patients 12 years of age and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy.[1]

Azedra, a high-specific iodine-131-metaiodobenzylguanidine (I-131 MIBG) product, is produced by a manufacturing process, Ultratrace®.[2] Compared with conventional I-131 MIBG, Azedra has little to no unlabeled MIBG. Theoretical advantages of using a high-specific activity product are improved targeting, greater tumor concentration, and decreased potential for side effects.[3,4]

The recommended Azedra regimen consists of one dosimetric dose and two therapeutic doses; the doses are administered via intravenous infusion.[1] Three scans are recommended after the dosimetric dose. Administration of the therapeutic doses may need to be reduced or delayed based on dosimetry data or adverse events (e.g., myelosuppression, pneumonitis). In one of the studies, patients received the first therapeutic dose 7 to 28 days after the dosimetric dose.[2] The two therapeutic doses should be separated by a minimum of 90 days.[1]

The administration of Azedra requires the use of pre- and concomitant medications.[1] Inorganic iodine therapy should be initiated before Azedra therapy and continued for 10 days after each Azedra dose. Fluid intake should be increased before Azedra therapy and continued for 1 week after each Azedra dose. Drugs that reduce catecholamine uptake or deplete catecholamine stores should be discontinued before Azedra therapy and should not be re-initiated for at least 7 days after each Azedra dose. Antiemetics are recommended before each Azedra dose.

DISEASE OVERVIEW

Pheochromocytoma is a rare tumor that develops in chromaffin cells in the central part of the adrenal glands. Paraganglioma also develops in chromaffin cells, but outside of the adrenal glands.[5-7] Most pheochromocytomas and paragangliomas are benign, but approximately 10% to 15% of pheochromocytomas and 20% to 50% of paragangliomas are malignant; cancer cells often migrate to the lymph nodes, bones, liver, or lungs.[5-8] Pheochromocytomas and paragangliomas release hormones, primarily adrenaline (epinephrine) and noradrenaline (norepinephrine) that cause episodic or persistent high blood pressure.[8] Hypertensive crisis can lead to cardiac arrhythmias, myocardial infarction, and death. Surgery is the standard of care for patients with localized or regional pheochromocytomas and paragangliomas.[5,6,8,9]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for Neuroendocrine and Adrenal Tumors (version 2.2020 – July 24, 2020) note surgical resection as the mainstay of treatment for benign and malignant pheochromocytomas and paragangliomas.[10] Azedra or other I-131 MIBG therapy (requires

positive MIBG scan) is recommended (among other therapies) for unresectable tumors or in the presence of distant metastases.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Azedra. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Azedra, as well as the monitoring required for adverse events and long-term efficacy, approval requires Azedra to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Azedra is recommended in those who meet one of the following criteria:

FDA-Approved Indications

21. Pheochromocytoma. Approve Azedra for 6 months if the patient meets ALL of the following conditions (A, B, and C):
- **C)** Patient is ≥ 12 years of age; AND
- **D)** Patient has iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma; AND
- **E)** The medication is prescribed by, or in consultation with, an oncologist or radiologist.

22. Paraganglioma. Approve Azedra for 6 months if the patient meets ALL of the following conditions (A, B, and C):
- **B)** Patient is ≥ 12 years of age; AND
- **C)** Patient has iobenguane scan positive, unresectable, locally advanced or metastatic paraganglioma; AND
- **D)** The medication is prescribed by, or in consultation with, an oncologist or radiologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Azedra is not recommended in the following situations:

270. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available

REFERENCES

1. Azedra® I 131 injection [prescribing information]. New York, NY: Progenics Pharmaceuticals, Inc.; August 2018.
2. Noto RB, Pryma DA, Jensen J, et al. Phase 1 study of high-specific-activity I-131 MIBG for metastatic and/or recurrent pheochromocytoma or paraganglioma. *J Clin Endocrinol Metab*. 2018;103:213-220.
3. Carrasquillo JA, Pandit-Taskar N, Chen CC. I-131 metaiodobenzylguanidine therapy of pheochromocytoma and paraganglioma. *Semin Nucl Med*. 2016;46:202-214.
4. Jimenez C. Treatment for patients with malignant pheochromocytomas and paragangliomas: a perspective from hallmarks of cancer. *Front Endocrinol*. 2018;9:277.
5. Pheochromocytoma. Available at: https://www.mayoclinic.org/diseases-conditions/pheochromocytoma/symptoms-causes/syc-20355367. Accessed on August 25, 2020.
6. Pheochromocytoma. Available at: https://emedicine.medscape.com/article/124059-overview. Updated July 20, 2020. Accessed on August 25, 2020.

7. Pappachan JM, Raskauskiene D, Sriraman R, et al. Diagnosis and management of pheochromocytoma: a practical guide to clinicians. *Curr Hypertens Rep*. 2014;16:442.
8. Pheochromocytoma and paraganglioma treatment (PDQ) – health professional version. Available at: https://www.cancer.gov/types/pheochromocytoma/hp/pheochromocytoma-treatment-pdq/. Updated September 26, 2019. Accessed on August 25, 2020.
9. Lenders JWM, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2014;99:1915-1942.
10. The NCCN Neuroendocrine and Adrenal Tumors Clinical Practice Guidelines in Oncology (Version 2.2020 – July 24, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 25, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/15/2018
Update	9/21/2018: Revised with new NCCN Neuroendocrine and Adrenal Tumors Clinical Practice Guidelines in Oncology (version 3.2018).	NA
Annual Revision	No criteria changes.	08/28/2019
Annual Revision	No criteria changes.	09/02/2020

NA – Not applicable.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Bavencio Prior Authorization Policy

- Bavencio® (avelumab injection for intravenous use – EMD Serono, Inc.)

REVIEW DATE: 07/15/2020

OVERVIEW

Bavencio, a programmed cell death ligand-1 (PD-L1) blocking antibody, is indicated for the treatment of the following:

- **Merkel cell carcinoma**, in adults and pediatric patients ≥ 12 years of age with metastatic disease.
- **Renal cell carcinoma**, in combination with Inlyta (axitinib tablets), for the first-line treatment of patients with advanced disease.
- **Urothelial carcinoma**, in patients with locally advanced or metastatic disease who have **a)** disease progression during or following platinum-containing chemotherapy; or **b)** have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; and for **c)** first-line maintenance treatment of locally advanced or metastatic disease that has not progressed with first-line platinum-containing chemotherapy.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on bladder cancer (version 5.2020 – May 12, 2020) recommends Bavencio as one of the "alternative preferred regimens" for subsequent therapy (category 2A) for locally advanced or metastatic disease (Stage IV, post-platinum).[2] It is recommended as second-line therapy for locally advanced or metastatic disease (stage IV) [post-platinum]. Bavencio can be used regardless of PD-L1 expression levels. The new indication in the maintenance setting after platinum therapy is not yet addressed in the guidelines. The NCCN Compendium[3] recommends Bavencio for urothelial carcinoma of the bladder; for upper genitourinary tract tumors (metastatic disease); urothelial carcinoma of the prostate (metastatic disease); and for primary carcinoma of the urethra (recurrent or metastatic disease).

The NCCN guidelines on Merkel cell carcinoma (version 1.2020 – October 2, 2019) recommends Bavencio as one of the options for disseminated disease (category 2A).[4] Clinical trial is preferred in this setting; but

other PD-1/PD-L1 inhibitor options for disseminated disease include Keytruda® (pembrolizumab for injection) and Opdivo® (nivolumab for injection) [all category 2A].

The NCCN guidelines for kidney cancer (version 2.2020 – August 5, 2019) recommends Bavencio in combination with Inlyta for first-line treatment in all risk group patients (favorable and poor/intermediate) for relapsed or Stage IV disease. It is one of the "other recommended regimens" for clear cell histology renal cell carcinoma with a category 2A recommendation. For subsequent therapy, Bavencio + Inlyta is a category 3 recommendation.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Bavencio. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Bavencio, as well as the monitoring required for adverse events and long-term efficacy, approval requires Bavencio to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Bavencio is recommended in those who meet the following criteria:

FDA-Approved Indication

5. Merkel Cell Carcinoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 12 years of age; AND
- **B)** Patient has metastatic (disseminated) Merkel cell carcinoma; AND
- **C)** The medication is prescribed by or in consultation with an oncologist.

2. Renal Cell Carcinoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient has relapsed or Stage IV clear cell disease; AND
- **B)** The medication will be used in combination with Inlyta (axitinib tablets); AND
- **C)** The medication is prescribed by or in consultation with an oncologist.

3. Urothelial Carcinoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient has locally advanced or metastatic urothelial carcinoma; AND
- **B)** Patient has tried platinum-containing chemotherapy (cisplatin or carboplatin); AND
- **C)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Bavencio is not recommended in the following situations:

271. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

10. Bavencio® injection for intravenous use [prescribing information]. Rockland, MA: EMD Serono, Inc.; June 2020.
11. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (Version 5.2020 – May 12, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed June 13, 2020.
12. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 12, 2020. Search term: avelumab.
13. The NCCN Merkel Cell Carcinoma Clinical Practice Guidelines in Oncology (Version 1.2020 – October 2, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed July 13, 2020.
14. The NCCN Kidney Cancer Clinical Practice Guidelines in Oncology (Version 2.2020 – August 5, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed July 13, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	New criteria	06/18/2019

Annual revision	• For all indications wherever Bavencio is mentioned in criteria, changed it to "The medication". • **Merkel Cell Carcinoma:** Instead of 12 years "or older", replaced with "≥". • **Renal Cell Carcinoma:** Deleted reference to "for first-line treatment" when used in combination with Inlyta.	07/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Beleodaq Prior Authorization Policy
- Beleodaq® (belinostat injection for intravenous use – Spectrum Pharmaceuticals)

REVIEW DATE: 09/02/2020

OVERVIEW
Beleodaq, a histone deacetylase inhibitor, is indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma.[1]

Guidelines
The National Comprehensive Cancer Network (NCCN) guidelines on T-Cell Lymphomas (version 1.2020 – January 6, 2020) recommends Beleodaq as a single-agent for second-line and subsequent therapy of peripheral T-cell lymphoma, adult T-cell leukemia/lymphoma, extranodal NK/T-cell lymphoma – nasal type, and hepatosplenic gamma – delta T-cell lymphoma.[2,3]

NCCN guidelines on Primary Cutaneous Lymphomas (version 2.2020 – April 10, 2020) recommend Beleodaq for systemic therapy of mycosis fungoides/Sezary syndrome and for primary cutaneous CD30+ T-cell lymphoproliferative disorders.[3,4]

POLICY STATEMENT
Prior authorization is recommended for prescription benefit coverage of Beleodaq. All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Beleodaq as well as the monitoring required for adverse events and long-term efficacy, approval requires Beleodaq to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Beleodaq is recommended in those who meet the following criteria:

FDA-Approved Indications

3. T-Cell Lymphoma. Approve for 1 year if Beleodaq is prescribed by or in consultation with an oncologist or a dermatologist.
Note: Examples include Peripheral T-Cell Lymphoma, Mycosis Fungoides/Sezary Syndrome, Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders, Adult T-Cell Leukemia/Lymphoma, Hepatosplenic Gamma-Delta T-Cell Lymphoma, Extranodal NK/T-Cell Lymphoma – Nasal Type

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Beleodaq is not recommended in the following situations:

166. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

531. Beleodaq® injection for intravenous use [prescribing information]. Irvine, CA: Spectrum Pharmaceuticals, Inc.; January 2020.
532. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 1.2020 – January 6, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed August 24, 2020.
533. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 24, 2020. Search term: belinostat.
534. The NCCN Primary Cutaneous Lymphomas Clinical Practice Guidelines in Oncology (Version 2.2020 – April 10, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed August 24, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	09/04/2019
Annual Revision	No criteria changes.	09/02/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Bendamustine Products Prior Authorization Policy

- Belrapzo™ (bendamustine injection for intravenous use – Eagle Pharmaceuticals)
- Bendeka® (bendamustine injection for intravenous use – Teva Pharmaceuticals, Inc.)
- Treanda® (bendamustine injection for intravenous use – Cephalon, Inc.)
- Bendamustine injection for intravenous use – various manufacturers

REVIEW DATE: 07/15/2020

Overview

Bendamustine, an alkylating agent, is indicated for the treatment of patients with:

- **B-cell non-Hodgkin lymphoma, indolent**, that has progressed during or within 6 months of treatment with rituximab or a rituximab containing regimen.
- **Chronic lymphocytic leukemia**. Efficacy compared to first-line agents other than chlorambucil has not been established.[1-3]

Guidelines

B-Cell Lymphomas

The National Comprehensive Cancer Network (NCCN) guidelines for B-cell lymphomas (version 2.2020 – July 9, 2020) recommend bendamustine for the treatment of a variety B-cell lymphomas, including follicular lymphoma (grade 1 and 2), gastric MALT lymphoma, nongastric MALT lymphoma, nodal marginal zone lymphoma, splenic marginal zone lymphoma, histologic transformation of marginal zone lymphoma to diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, DLBCL, high-grade B-cell lymphoma, acquired immunodeficiency syndrome (AIDS)-related B-cell lymphoma, and post-transplant lymphoproliferative disorders.[4,6] Bendamustine is recommended as monotherapy, or in combination with rituximab, Polivy™ (polatuzumab vedotin-piiq injection for intravenous use), or Gazyva depending on the lymphoma type and previous treatment history.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

The NCCN guidelines for chronic lymphocytic leukemia/small lymphocytic lymphoma (version 4.2020 – December 20, 2019) recommend bendamustine, in combination with rituximab (e.g., Rituxan, Truxima), Gazyva® (obinutuzumab injection for intravenous [IV] use), or Arzerra® (ofatumumab injection for IV use), for the first-line treatment of patients ≥ 65 years of age without del(17p)/TP53 mutation, or younger patients with or without significant comorbidities.[4,5] Bendamustine in combination with rituximab is recommended for the treatment of relapsed or refractory disease without del(17p)/TP53 mutation in patients ≥ 65 years of age, or in patients < 65 years of age with or without significant comorbidities.

Hodgkin Lymphoma

The NCCN guidelines for Hodgkin lymphoma (version 2.2020 – April 17, 2020) recommend bendamustine for the treatment of recurrent or refractory classic Hodgkin Lymphoma.[4,7] In patients ≥ 18 years of age, bendamustine in combination with gemcitabine and vinorelbine, or in combination with Adcetris® (brentuximab injection for IV use) is recommended for second-line or subsequent therapy (if not previously used), or in combination with carboplatin and etoposide for third-line or subsequent therapy, or as a single agent for subsequent therapy. In patients > 60 years of age, bendamustine is recommended as a single agent for palliative therapy of relapsed or refractory disease.

Multiple Myeloma

Bendamustine is recommended in the NCCN guidelines for multiple myeloma (version 4.2020 – May 8, 2020) as a treatment option for relapsed or progressive multiple myeloma.[4,8] Bendamustine is recommended as a single agent, or in combination with dexamethasone and Revlimid® (lenalidomide capsules) or with dexamethasone and Velcade® (bortezomib injection for IV and subcutaneous use).

Primary Cutaneous Lymphomas

The NCCN guidelines for primary cutaneous lymphomas (version 2.2020 – April 10, 2020) recommend bendamustine for the systemic treatment of mycosis fungoides/Sezary syndrome with or without skin-directed or radiation therapy, and as a single agent for the treatment of relapsed/refractory primary cutaneous CD30+ T-cell lymphoproliferative disorders.[4,9]

T-Cell Lymphomas

The NCCN guidelines for T-cell lymphomas (version 1.2020 – January 6, 2020) recommend bendamustine as a single agent for the treatment of relapsed or refractory peripheral T-cell lymphomas, adult T-cell leukemia/lymphoma, and refractory hepatosplenic gamma-delta T-cell lymphoma as subsequent therapy.[4,10]

Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma

Bendamustine is recommended in the NCCN guidelines for Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma (version 2.2020 – April 15, 2020) as a single agent or in combination with rituximab for primary treatment, for the treatment of previously treated disease that did not respond, or for progressive or relapsed disease.[4,11]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of bendamustine. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with bendamustine as well as the monitoring required for adverse events and long-term efficacy, approval requires bendamustine to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of bendamustine is recommended in those who meet the following criteria:

FDA-Approved Indications

9. B-Cell Non-Hodgkin Lymphoma. Approve for 6 months if bendamustine is prescribed by or in consultation with an oncologist.

10. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Approve for 6 months if bendamustine is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

11. Hodgkin Lymphoma. Approve for 6 months if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Bendamustine is used as second-line or subsequent therapy; AND
- **C)** Bendamustine is prescribed by or in consultation with an oncologist.

12. Multiple Myeloma. Approve for 6 months if the patient meets the following criteria (A and B):
- **A)** Patient has relapsed or refractory disease; AND
- **B)** Bendamustine is prescribed by or in consultation with an oncologist.

13. T-Cell Lymphoma. (Note: Examples include Peripheral T-Cell Lymphoma, Mycosis Fungoides/Sezary Syndrome, Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders, Adult T-Cell Leukemia/Lymphoma, Hepatosplenic Gamma-Delta T-Cell Lymphoma). Approve for 6 months if bendamustine is prescribed by or in consultation with an oncologist.

14. Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma. Approve for 6 months if bendamustine is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of bendamustine is not recommended in the following situations:

167. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

535. Bendeka® [prescribing information]. North Wales, PA: Teva Pharmaceuticals, Inc.; October 2019.
536. Treanda® [prescribing information]. Frazer, PA: Cephalon; November 2019.
537. Belrapzo™ [prescribing information]. Woodcliff Lake, NJ: Eagle Pharmaceuticals, Inc.; October 2019.
538. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 6, 2020. Search term: bendamustine.
539. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (version 4.2020 – December 20, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 6, 2020.
540. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 1.2020 – January 22, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 6, 2020.
541. The NCCN Hodgkin Lymphoma Clinical Practice Guidelines in Oncology (version 2.2020 – April 17, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 6, 2020.
542. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (version 4.2020 – May 8, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 6, 2020.
543. The NCCN Primary Cutaneous Lymphomas Clinical Practice Guidelines in Oncology (version 2.2020 – April 10, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 6, 2020.
544. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 1.2020 – January 6, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 6, 2020.
545. The NCCN Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma Clinical Practice Guidelines in Oncology (version 2.2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 6, 2020.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	07/17/2019
Annual revision	No criteria changes.	07/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Besponsa Prior Authorization Policy

- Besponsa™ (inotuzumab ozogamicin injection for intravenous use – Pfizer)

REVIEW DATE: 07/15/2020

OVERVIEW

Besponsa, an antibody-drug conjugate directed against human CD22, is indicated for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for ALL (version 1.2020 – January 15, 2020) recommend Besponsa for the treatment of relapsed/refractory Philadelphia chromosome negative (Ph-) B-cell ALL, or relapsed/refractory Philadelphia chromosome positive (Ph+) B-cell ALL with tyrosine kinase inhibitor intolerant or refractory disease, as a single agent or in combination with mini-hyper CVD (cyclophosphamide, dexamethasone, vincristine, methotrexate, cytarabine).[2,3]

The NCCN guidelines on pediatric ALL (version 2.2020 – November 25, 2019) recommend Besponsa as a single-agent for the treatment of pediatric patients with relapsed/refractory Ph- B-cell ALL, or relapsed/refractory Ph+ B-cell ALL with tyrosine kinase inhibitor intolerant or refractory disease.[4]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Besponsa. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Besponsa as well as the monitoring required for adverse events and long-term efficacy, approval requires Besponsa to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Besponsa is recommended in those who meet the following criteria:

FDA-Approved Indications

4. **Acute Lymphoblastic Leukemia.** (Note: This applies to Philadelphia chromosome positive and negative acute lymphoblastic leukemia.) Approve for 6 months if the patient meets the following criteria (A and B):

D) Patient has relapsed or refractory, B-cell precursor acute lymphoblastic leukemia; AND

E) Besponsa is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Besponsa is not recommended in the following situations:

168. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

546. Besponsa™ injection for intravenous use [prescribing information]. Philadelphia, PA: Pfizer; August 2017.
547. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (Version 1.2020 – January 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed July 7, 2020.
548. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 7, 2020. Search term: inotuzumab.
549. The NCCN Pediatric Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (Version 2.2020 – November 25, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed July 7, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/17/2019
Annual review	**Acute lymphoblastic leukemia.** Removed criteria for Besponsa use as a single agent.	07/15/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Bevacizumab Products Prior Authorization Policy

- Avastin® (bevacizumab injection for intravenous injection – Genentech, Inc.)
- Mvasi™ (bevacizumab-awwb injection for intravenous infusion – Amgen)
- Zirabev™ (bevacizumab-bvzr injection for intravenous infusion – Pfizer)

REVIEW DATE: 03/17/2021

OVERVIEW

Bevacizumab is a recombinant humanized monoclonal antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF), a key mediator of angiogenesis.[1] Bevacizumab is indicated for the following uses:

- **Cervical cancer** (persistent, recurrent, or metastatic), in combination with paclitaxel and cisplatin OR paclitaxel and topotecan.
- **Colorectal cancer (CRC)**, metastatic, in combination with intravenous 5-fluorouracil [5-FU]-based chemotherapy for first- or second-line treatment; or for mCRC, in combination with fluoropyrimidine (5-FU, capecitabine)-irinotecan-based or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab-containing regimen; Limitation of use: Bevacizumab is not indicated for adjuvant treatment of colon cancer.
- **Glioblastoma**, treatment of recurrent disease in adults.
- **Hepatocellular carcinoma (HCC)**: Bevacizumab in combination with Tecentriq (atezolizumab injection for intravenous use) is indicated for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy.
- **Non-small cell lung cancer (NSCLC)**, non-squamous, in combination with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent or metastatic disease.

- **Ovarian (epithelial), fallopian tube, or primary peritoneal cancer**, recurrent disease, that is platinum-resistant in combination with paclitaxel, Doxil® (doxorubicin liposome intravenous infusion; i.e., pegylated liposomal doxorubicin), or topotecan for the treatment of patients who received no more than two prior chemotherapy regimens, OR disease that is platinum-sensitive in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by bevacizumab as a single agent; or in combination with carboplatin and paclitaxel, followed by bevacizumab as a single agent, in patients with stage III or IV disease following initial surgical resection.
- **Renal cell carcinoma (mRCC)**, metastatic, in combination with interferon alfa subcutaneous injection.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of bevacizumab in patients with conditions other than ophthalmic. The intent of this policy is to provide recommendations for uses other than ophthalmic conditions. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with bevacizumab as well as the monitoring required for adverse events and long-term efficacy, approval requires bevacizumab to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of bevacizumab products is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Central Nervous System Tumors.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** The medication is prescribed by or in consultation with an oncologist; AND
   - **B)** Patient has tried at least one previous therapy; AND
     Note: Examples are temozolomide capsules or injection, etoposide, carmustine, radiotherapy.
   - **C)** Patient has ONE of the following (i, ii, iii, or iv):
     - **i.** Anaplastic gliomas; OR
     - **ii.** Glioblastoma; OR
     - **iii.** Intracranial and spinal ependymoma (excluding subependymoma) in patient ≥ 18 years of age; OR
     - **iv.** Meningiomas.

2. **Cervical Cancer.** Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** The medication is prescribed by or in consultation with an oncologist; AND
   - **B)** Patient has recurrent or metastatic cervical cancer.

3. **Colon or Rectal Cancer.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
   - **A)** The medication is prescribed by or in consultation with an oncologist; AND
   - **B)** Patient has advanced or metastatic colon or rectal cancer [Stage IV]; AND
   - **C)** The medication is used in combination with a chemotherapy regimen; AND
     Note: Examples of chemotherapy regimens are 5-fluorouracil with leucovorin, and may include one or both of oxaliplatin, irinotecan; capecitabine with or without oxaliplatin; irinotecan with or without oxaliplatin.
   - **D)** Bevacizumab is not being used for adjuvant treatment of colon cancer.

4. **Hepatocellular Carcinoma (HCC).** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** Bevacizumab is prescribed by or in consultation with an oncologist; AND
   - **B)** The medication is used in combination with Tecentriq (atezolizumab injection); AND

C) Patient has not received prior systemic therapy.

5. Non-Small Cell Lung Cancer (NSCLC). Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** The medication is prescribed by or in consultation with an oncologist; AND
- **B)** Patient has advanced or metastatic non-squamous NSCLC (i.e., adenocarcinoma, large cell, or NSCLC not otherwise specified) and meets ONE of the following criteria (i, ii, iii, or iv):
  - **i.** The NSCLC tumor is positive for epidermal growth factor receptor (*EGFR*) mutation and bevacizumab is used in combination with erlotinib; OR
  - **ii.** Patient has previously received targeted drug therapy for an actionable mutation; OR
    Note: Examples of actionable mutations include sensitizing epidermal growth factor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, *RET* rearrangement positive, *MET* exon 14 skipping, *NTRK* gene fusion positive, *BRAF V600E* mutation positive, and ROS proto-oncogene 1 (*ROS1*) rearrangement positive.
  - **iv.** The NSCLC tumor is negative or unknown for actionable mutations and the patient meets ONE of the following criteria (a or b):
    Note: Examples of actionable mutations include sensitizing epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, *RET* rearrangement positive, *MET* exon 14 skipping, *NTRK* gene fusion positive, *BRAF V600E* mutation positive, and ROS proto-oncogene 1 [*ROS1*] rearrangement positive.
    - **a)** Bevacizumab is used as initial therapy in combination with other systemic therapies; OR
      Note: Examples of systemic therapies are cisplatin, carboplatin, Tecentriq (atezolizumab for intravenous use), Alimta (pemetrexed for intravenous use), paclitaxel.
    - **b)** Bevacizumab is used as subsequent therapy.
      Note: Bevacizumab can be used either as a single agent or in combination with other agents.

6. Ovarian, Fallopian Tube, or Primary Peritoneal Cancer. Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

7. Renal Cell Cancer. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** The medication is prescribed by or in consultation with an oncologist; AND
- **B)** Patient has advanced (e.g., relapsed, metastatic, or Stage IV) renal cell cancer.

Other Uses with Supportive Evidence

8. Breast Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** The medication is prescribed by or in consultation with an oncologist; AND
- **B)** Patient has recurrent or metastatic human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
- **C)** The medication is used in combination with paclitaxel.

9. Endometrial Carcinoma. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** The medication is prescribed by or in consultation with an oncologist; AND
- **B)** Patient has progressed on prior chemotherapy.
  Note: Examples of chemotherapy are carboplatin, cisplatin, paclitaxel, docetaxel, doxorubicin.

10. Malignant Pleural Mesothelioma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Bevacizumab is prescribed by or in consultation with an oncologist; AND
- **B)** Patient has unresectable malignant pleural mesothelioma; AND
- **C)** One of the following applies (i or ii):
  - **i.** Bevacizumab will be used in combination with a chemotherapy regimen; OR
    Note: Examples of chemotherapy regimens are Alimta [pemetrexed injection], cisplatin, carboplatin.

ii. Bevacizumab is being used as a single agent for maintenance therapy after the patient has received combination chemotherapy regimen.
Note: Examples of chemotherapy regimens are Alimta [pemetrexed injection], cisplatin, carboplatin.

11. **Neovascular or Vascular Ophthalmic Conditions.** Approve for 3 years.
    Note: Examples of neovascular or vascular ophthalmic conditions include diabetic macular edema (includes patients with diabetic retinopathy and diabetic macular edema), macular edema following retinal vein occlusion, myopic choroidal neovascularization, neovascular (wet) age-related macular degeneration, other neovascular diseases of the eye (e.g., neovascular glaucoma, retinopathy of prematurity, sickle cell neovascularization, choroidal neovascular conditions).

12. **Small Bowel Adenocarcinoma.** Approve for 1 year if the patient meets the following criteria (A and B):
    A) The medication is prescribed by or in consultation with an oncologist; AND
    B) The medication is used in combination with chemotherapy.
    Note: Examples of chemotherapy are fluorouracil, leucovorin, and oxaliplatin (FOLFOX), capecitabine and oxaliplatin (CapeOX), fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI).

13. **Soft Tissue Sarcoma.** Approve for 1 year if the patient meets BOTH of the following criteria (A and B):
    A) Patient has angiosarcoma or solitary fibrous tumor; AND
    B) The medication is prescribed by or in consultation with an oncologist.

14. **Vulvar Cancer (Squamous Cell Carcinoma).** Approve for 1 year if the patient meets the following criteria (A and B):
    A) The medication is prescribed by or in consultation with an oncologist; AND
    B) Bevacizumab is used in combination with a chemotherapy regimen.
    Note: Examples of chemotherapy regimens are cisplatin and paclitaxel, carboplatin and paclitaxel.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of bevacizumab products is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Avastin® solution for intravenous infusion [prescribing information]. South San Francisco, CA: Genentech, Inc. December 2017.
2. The NCCN Cervical Cancer Clinical Practice Guidelines in Oncology (version 1.2021 – October 2, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 15, 2021.
3. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 2.2021 – January 21, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 15, 2021.
4. The NCCN Drugs & Biologics Compendium. © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 15, 2021. Search term: bevacizumab.
5. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 1.2021 – December 22, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 15, 2021.
6. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (Version 3.2020 – September 11, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 15, 2021.
7. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 4.2021 – March 3, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 15, 2021.
8. The NCCN Ovarian Cancer Clinical Practice Guidelines in Oncology (version 1.2021 – February 26, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org Accessed on March 15, 2021.
9. Escudier B, Pluzanska A, Koralewski P, et al; AVOREN Trial investigators. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet.* 2007;370:2103-2111.
10. Rini BI, Halabi S, Rosenberg JE, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. *J Clin Oncol.* 2010;28:2137-2143.

11. The NCCN Kidney Cancer Clinical Practice Guidelines in Oncology (version 2.2021 – February 3, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed March 15, 2021.
12. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 2.2021 – March 12, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed March 15, 2021.
13. The NCCN Malignant Pleural Mesothelioma Clinical Practice Guidelines in Oncology (version 2.2021 – February 16, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed March 15, 2021.
14. The NCCN Small Bowel Adenocarcinoma Clinical Practice Guidelines in Oncology (version 1.2021 – February 16, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed March 15, 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	03/27/2019
Selected Revision	Addition of Zirabev™ (bevacizumab-bvzr solution for intravenous infusion – Pfizer) to the product list. Ophthalmic conditions are no longer targeted in this policy. A new indication of **Neovascular and Vascular Ophthalmic Conditions** was created to combine all indication previously listed in the policy. All requests for ophthalmic indications are to approve for 1 year. • **Diabetic Macular Edema (Includes Patients with Diabetic Retinopathy and Diabetic Macular Edema).** Existing criteria was removed. This indication was placed within the new indication of **Neovascular and Vascular Ophthalmic Conditions.** • **Endometrial Cancer.** Added new condition for approval. Previously, this condition was listed under Other Cancer-Related Indications. • **Macular Edema Following Retinal Vein Occlusion.** Existing criteria was removed. This indication was placed within the new indication of **Neovascular and Vascular Ophthalmic Conditions.** • **Myopic Choroidal Neovascularization.** Existing criteria was removed. This indication was placed within the new indication of **Neovascular and Vascular Ophthalmic Conditions.** • **Neovascular (Wet) Age-Related Macular Degeneration.** Existing criteria was removed. This indication was placed within the new indication of **Neovascular and Vascular Ophthalmic Conditions.** • **Other Neovascular Diseases of the Eye (e.g., neovascular glaucoma, retinopathy of prematurity, sickle cell neovascularization, choroidal neovascular conditions).** Existing criteria was removed. This indication was placed within the new indication of **Neovascular and Vascular Ophthalmic Conditions.** • **Small Bowel Adenocarcinoma.** Added new condition for approval based on guideline recommendations. • **Soft Tissue Sarcoma.** Added new condition for approval. Previously, this was listed under Other Cancer-Related Indications. • **Other Cancer-Related Indications.** Deleted this indication. Listed out conditions as separate criteria.	09/11/2019
Selected Revision	Approval duration for **Neovascular or Vascular Ophthalmic Conditions** was changed from 1 year to 3 years.	11/06/2019
Annual Revision	• **Non-Small Cell Lung Cancer (NSCLC).** Added new criteria for bevacizumab use in EGFR mutation-positive NSCLC in combination with erlotinib in first-line setting.	04/01/2020
Selected Revision	• Added new FDA-approval indication for hepatocellular carcinoma	06/10/2020
Annual Revision	• **Central Nervous System Tumors:** Moved the subtypes of tumors from indication to criteria. Changed patient has tried "one other therapy" to "one previous therapy". Added carmustine and etoposide to existing examples in Note. For Intracranial and spinal ependymoma subtype, deleted reference to "adults" and instead added "in patient ≥ 18 years of age". • **Non-Small Cell Lung Cancer:** Changed "targetable" mutations to "actionable" mutations. For bevacizumab use in combination with erlotinib, deleted criteria requiring "as first-line therapy". Modified criteria requiring use of at least one targeted therapy (if positive for actionable mutation), to state "patient has previously received targeted drug therapy for an actionable mutations". Moved actionable mutations to list as examples in a new Note and added new actionable mutations *RET* rearrangement positive, *MET* exon 14 skipping, *NTRK* gene fusion positive, *BRAF*	03/17/2021

	V600E mutation positive to the list. Deleted criteria referring to NSCLC tumor that is *BRAF V600E* mutation-positive and bevacizumab use as either first-line or subsequent therapy. This is not needed due to the modified criteria regarding targeted drug therapy for actionable mutation. For criteria referring to negative or unknown actionable mutations, moved examples to new Note and updated the list of actionable mutations as above. Previous criteria referring to bevacizumab use specifically in combination with "platinum therapies" was deleted and instead criteria was modified to say "with other systemic therapies". A new Note has been added with examples of systemic therapies. For the other criteria referring to bevacizumab use as subsequent therapy, the criteria referring to "and is used as a single agent or in combination with other agents" was moved to a new Note. • **Soft Tissue Sarcoma:** Moved the subtypes angiosarcoma and solitary fibrous tumor from indication to criteria. Deleted reference to hemangiopericytoma since it is no longer in guidelines.	

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Blenrep Prior Authorization Policy

- Blenrep™ (belantamab mafodotin-blmf intravenous infusion – GlaxoSmithKline)

REVIEW DATE: 08/13/2020

OVERVIEW

Blenrep, a B-cell maturation antigen-directed antibody and microtubule inhibitor conjugate, is indicated for treatment of adults with relapsed or refractory multiple myeloma, in those who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. This indication was approved under accelerated approval based on response rate. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trial(s). It is administered as a 2.5 mg/kg intravenous infusion given once every 3 weeks.

Guidelines

Blenrep has not yet been addressed in guidelines for multiple myeloma. National Comprehensive Cancer Network (NCCN) guidelines for multiple myeloma (version 4.2020 – May 8, 2020) recommend various regimens as primary therapy (transplant eligible and non-transplant candidates), maintenance therapy, and previously treated multiple myeloma.[2] The choice of regimen takes into account patient factors as well as response and tolerability to previous regimens. Triplet regimens (e.g., with a proteasome inhibitor, immunomodulatory drug, and corticosteroid) are standard therapy for multiple myeloma. Blenrep is an other recommended regimen for its approved use in relapsed/refractory disease. Other available therapies used as monotherapy or in combination regimens include agents from the following drug classes:

- Proteasome inhibitors (e.g., Velcade® [bortezomib injection], Kyprolis® [carfilzomib injection], Ninlaro® [ixazomib capsules]);
- Immunomodulatory drugs (e.g., Thalomid® [thalidomide capsules], Revlimid® [lenalidomide capsules], Pomalyst® [pomalidomide capsules]);
- Steroids (e.g., dexamethasone, prednisone);
- CD38-directed monoclonal antibodies (Darzalex® [daratumumab intravenous infusion], Darzalex Faspro™ [daratumumab and hyaluronidase-fihj subcutaneous injection], Sarclisa® (isatuximab-irfc intravenous infusion]);
- Histone deacetylase inhibitor (Farydak® [panobinostat capsules]);
- Signaling Lymphocytic Activation Molecule Family member 7-directed immunostimulatory antibody (Empliciti® [elotuzumab injection]);
- Nuclear export inhibitor (Xpovio™ [selinexor tablets]);

- Alkylating agents (e.g., cyclophosphamide, melphalan); and
- Other cytotoxic drugs (e.g., vincristine, doxorubicin, liposomal doxorubicin).

Safety

Blenrep may cause changes in the corneal epithelium resulting in vision changes, including severe vision loss and corneal ulcer. The patient may experience symptoms such as blurred vision and dry eyes. Ophthalmic examinations should be conducted at baseline and prior to each dose, and promptly upon worsening of symtoms. Blenrep should be withheld until improvement and resumed or permanently discontinued based on the severity. Due to risks of ocular toxicity, there is a Risk Evaluation and Mitigation Strategy (REMS) program for Blenrep. Included in the program is a requirement for prescribers to be certified and counsel patients regarding ocular toxicity and the need for ophthalmic examinations prior to each dose. Patients must also be enrolled in the REMS and comply with monitoring.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Blenrep. All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Blenrep as well as the monitoring required for adverse events and long-term efficacy, approval requires Blenrep to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Blenrep is recommended in those who meet the following criteria:

FDA-Approved Indications

5. Multiple Myeloma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
- **15.** Patient is ≥ 18 years of age; AND
- **16.** Patient has tried at least four prior systemic lines of therapy; AND
- **17.** Among the previous therapies tried, the patient has received at least one drug from each of the following classes (i, ii, and iii):
  - **i.** Proteasome inhibitor; AND
    Note: Examples include Velcade (bortezomib injection), Kyprolis (carfilzomib infusion), Ninlaro (ixazomib capsules).
  - **ii.** Immunomodulatory drug; AND
    Note: Examples include Revlimid (lenalidomide capsules), Pomalyst (pomalidomide capsules), Thalomid (thalidomide capsules).
  - **iii.** Anti-CD38 monoclonal antibody; AND
    Note: For example, Darzalex (daratumumab infusion), Darzalex Faspro (daratumumab and hyaluronidase-fihj subcutaneous injection), or Sarclisa (isatuximab-irfc infusion).
- **18.** The agent will be prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Blenrep is not recommended in the following situations:

169. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

550. Blenrep™ intravenous infusion [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; August 2020.
551. Clinical Practice Guidelines in Oncology (Version 1.2021 – August 24, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 25, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/13/2020
Update	08/25/2020: No changes to the criteria. Update the Overview to include recently updated guidelines that now address Blenrep.	NA

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Blincyto Prior Authorization Policy

- Blincyto® (blinatumomab injection for intravenous use – Amgen)

REVIEW DATE: 09/02/2020

OVERVIEW

Blincyto, a bispecific CD19-directed CD3 T-cell engager, is indicated for the treatment of adults and children with:

- B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) $\geq$ 0.1%.[1] Accelerated approval was granted for this indication based on MRD response and hematologic relapse-free survival. Continued approval may be dependent on verification and description of clinical benefit in confirmatory trials.
- Relapsed or refractory B-cell ALL.[1]

Blincyto contains a boxed warning for Cytokine Release Syndrome which may be life-threatening or fatal and Neurologic toxicities which may be severe, life-threatening or fatal.[1] Stop or discontinue Blincyto as recommended for either toxicity.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on Acute Lymphoblastic Leukemia (version 1.2020 – January 15, 2020) and Pediatric Acute Lymphoblastic Leukemia (version 2.2020 – November 25, 2019) guidelines recommend Blincyto as single-agent therapy for relapsed/refractory B-cell ALL; consolidation therapy in adolescents, young adults, and adults with positive MRD after complete response to induction therapy; and for pediatric patients with MRD positive disease, less than complete response, or high-risk genetics.[2-4]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Blincyto. All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Blincyto, as well as the monitoring required for adverse events and long-term efficacy, approval requires Blincyto to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Blincyto is recommended in those who meet the following criteria:

FDA-Approved Indications

161. Acute Lymphoblastic Leukemia. Approve for 1 year if the patient meets the following criteria (A, B, and C):

F) Patient has B-cell precursor disease; AND

G) Patient meets one of the following (i or ii):
- **a.** Patient is Philadelphia chromosome negative and meets one of the following (a or b):
  - **a)** Patient has relapsed or refractory disease; OR
  - **b)** Patient is minimal residual disease positive; OR
- **b.** Patient is Philadelphia chromosome positive and meets one of the following (a, b, c, or d):
  - **a)** Patient has tried at least one tyrosine kinase inhibitor (TKI) used for the treatment of acute lymphoblastic leukemia; OR
    Note: Examples of a TKI include Gleevec® (imatinib tablets), Sprycel® (dasatinib tablets), Tasigna® (nilotinib capsules).
  - **b)** Patient does not have a complete response to induction therapy; OR
  - **c)** Patient is minimal residual disease positive; OR
  - **d)** Patient has high-risk genetics; AND

H) Blincyto is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Blincyto is not recommended in the following situations:

170. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

552. Blincyto® injection for intravenous use [prescribing information]. Thousand Oaks, CA: Amgen; March 2020.
553. The NCCN Pediatric Acute Lymphoblastic Leukemia Oncology Guidelines (Version 2.2020 – November 25, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed August 24, 2020.
554. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (Version 1.2020 – January 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed August 24, 2020.
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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	09/04/2019
Annual Revision	No criteria changes.	09/02/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Bortezomib (Velcade) Prior Authorization Policy

- Velcade® (bortezomib intravenous or subcutaneous injection – Millennium Pharmaceuticals, generics [intravenous only])

REVIEW DATE: 10/14/2020; selected revision 01/20/2021

OVERVIEW

Bortezomib, a proteasome inhibitor, is indicated in adults with the following conditions:[1]

- **Mantle cell lymphoma**.
- **Multiple myeloma**.

Guidelines

Bortezomib is mentioned in several guidelines published by the National Comprehensive Cancer Network (NCCN).

- **Acute lymphoblastic leukemia:** Guidelines for pediatric disease (version 1.2021 – September 16, 2020) include bortezomib-based regimens among the other recommended regimens for relapsed or refractory disease.
- **AIDS** (**acquired immune deficiency syndrome)-related Kaposi sarcoma:** Guidelines (version 3.2020 – July 15, 2020) include bortezomib among the other recommended regimens for patients who have relapsed/refractory disease.
- **B-cell lymphomas:** Guidelines for B cell lymphoma (version 4.2020 – August 13, 2020) recommend bortezomib (as a component of (VR-CAP [bortezomib/Rituxan/cyclophosphamide/doxorubicin/prednisone]) as a preferred less aggressive therapy option for the initial treatment of patients (induction therapy) with newly diagnosed mantle cell lymphoma.[10] VR-CAP, bortezomib/bendamustine/rituximab, and bortezomib ± rituximab are also listed as second-line therapies for relapsed or refractory mantle cell lymphoma. For patients with relapsed or refractory Castleman's disease, bortezomib ± rituximab is listed among the treatment options.
- **Classic Hodgkin lymphoma:** Guidelines for pediatric disease (version 1.2021 – September 28, 2020) include bortezomib/ifosfamide/vinorelbine among the subsequent therapy options for relapsed or refractory disease.
- **Multiple myeloma:** Bortezomib features prominently in the NCCN Multiple Myeloma clinical practice guidelines (version 2.2021 – September 9, 2020).[3] Various bortezomib-containing regimens are listed as Preferred for primary therapy (transplant and nontransplant candidates) and previously treated disease. Bortezomib is also a component of multiple other regimens across the spectrum of disease. For maintenance therapy, bortezomib ± Revlimid (lenalidomide capsules) are also listed as treatment options.
- **Systemic light chain amyloidosis:** Guidelines (version 1.2021 – September 1, 2020) list bortezomib alone or in combination with other agents for primary therapy (transplant and non-transplant candidates) and previously treated disease.[11] NCCN notes that bortezomib was well tolerated at doses up to 1.6 mg/m^2 on a once-weekly schedule and 1.3 mg/m^2 on a twice-weekly schedule. The once-weekly regimen was associated with lower neurotoxicity.
- **Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma:** Guidelines (version 1.2021 – September 1, 2020) recommend the following bortezomib-based regimens for primary therapy and for previously treated disease: bortezomib ± Rituxan, bortezomib/dexamethasone, and bortezomib/dexamethasone/Rituxan.[15]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of bortezomib. All approvals are provided for the duration noted below. Because of the of the specialized skills required for evaluation and diagnosis of patients treated with bortezomib, as well as the monitoring required for adverse events and long-term efficacy, approval requires bortezomib to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

6. Mantle Cell Lymphoma. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient meets ONE of the following criteria (i or ii):

i. Patient has previously tried at least one other therapy for mantle cell lymphoma; OR
Note: Examples of other therapies for mantle cell lymphoma include regimens containing a rituximab product, cytarabine, cisplatin, cyclophosphamide, doxorubicin, vincristine, or bendamustine.

ii. The medication is used in combination with at least one other agent; AND
Note: Examples of other agents used in combination with bortezomib for mantle cell lymphoma include a rituximab product, bendamustine, cyclophosphamide, and doxorubicin.

B) The medication is prescribed by or in consultation with an oncologist or a hematologist.

7. Multiple Myeloma. Approve for 1 year if the patient meets BOTH of the following (A and B):

19. Patient meets ONE of the following criteria (i or ii):

i. The medication will be used in combination with at least one other agent; OR
Note: Examples of other agents that may be used in combination with Velacade include dexamethasone, cyclophosphamide, doxorubicin, Doxil® (doxorubicin liposomal injection), Revlimid® (lenalidomide capsules), Thalomid® (thalidomide capsules), cisplatin, etoposide, Darzalex® (daratumumab for injection), Pomalyst (pomalidomide capsules), bendamustine, Empliciti® (elotuzumab for injection), Farydak® (panobinostat capsules).

ii. The medication is being used for maintenance therapy; AND

20. The medication is prescribed by or in consultation with an oncologist or a hematologist.

Other Uses with Supportive Evidence

8. Acute Lymphoblastic Lymphoma. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient has relapsed or refractory disease; AND

B) The medication is prescribed by or in consultation with an oncologist.

9. AIDS (Acquired Immune Deficiency Syndrome)-Related Kaposi Sarcoma. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient has tried at least one systemic chemotherapy; AND
Note: Examples of systemic chemotherapies for AIDS-related Kaposi sarcoma include doxorubicin and paclitaxel.

B) The medication is prescribed by or in consultation with an oncologist.

10. Castleman's Disease. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient has relapsed, refractory, or progressive disease; AND

B) The medication is prescribed by or in consultation with an oncologist.

11. Classic Hodgkin Lymphoma. Approve for 1 year if the patient meets the following (A and B):

A) Patient has tried at least one systemic chemotherapy regimen; AND
Note: Examples of systemic chemotherapies used in regimens for Hodgkin lymphoma include doxorubicin, bleomycin, vincristine, etoposide, and dacarbazine.

B) The medication is prescribed by or in consultation with an oncologist.

12. Systemic Light Chain Amyloidosis. Approve for 1 year if prescribed by or in consultation with an oncologist or a hematologist.

13. Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma. Approve for 1 year if prescribed by or in consultation with an oncologist or a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of bortezomib is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

15. Velcade® injection for subcutaneous or intravenous use [prescribing information]. Cambridge, MA: Millennium Pharmaceuticals, Inc.; April 2019.
16. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 6, 2020. Search term: bortezomib.
17. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (Version 2.2021 – September 9, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 5, 2020.
18. Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomized, open-label, phase 3 trial. *Lancet.* 2017;389:519-527.
19. Niesvizky R, Flinn IW, Rifkin R, et al. Community-based Phase IIIB trial of three UPFRONT bortezomib-based myeloma regimens. *J Clin Oncol.* 2015;33:3921-3929.
20. Kumar S, Flinn I, Richardson PG, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. *Blood.* 2012;119:4375-4382.
21. Goy A, Bernstein SH, Kahl BS, et al. Bortezomib in patients with relapsed or refractory mantle cell lymphoma: updated time-to-event analyses of the multicenter phase 2 PINNACLE study. *Ann Oncol.* 2009;20:520-525.
22. Friedberg JW, Vose JM, Kelly JL, et al. The combination of bendamustine, bortezomib, and rituximab for patients with relapsed/refractory indolent and mantle cell non-Hodgkin lymphoma. *Blood.* 2011;117:2807-2812.
23. Lamm W, Kaufmann H, Raderer M, et al. Bortezomib combined with rituximab and dexamethasone is an active regimen for patients with relapsed and chemotherapy-refractory mantle cell lymphoma. *Haematologica.* 2011;96:1008-1014.
24. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 4.2020 – August 13, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed October 6, 2020.
25. The NCCN Systemic Light Chain Amyloidosis Clinical Practice Guidelines in Oncology (Version 1.2021 – September 1, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed October 6, 2020.
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28. Reece DE, Hegenbart U, Sanchorawala V, et al. Long-term follow-up from a phase 1/2 study of single-agent bortezomib in relapsed systemic AL amyloidosis. *Blood.* 2014;124:2498-2506.
29. The NCCN Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma Clinical Practice Guidelines in Oncology (Version 1.2021 – September 1, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed October 6, 2020.
30. Leblebjian H, Noonan K, Paba-Prada C, et al. Cyclophosphamide, bortezomib, and dexamethasone combination in Waldenstrom macroglobulinemia. Correspondence. *Am J Hematol.* 2015;90:E122.
31. Ghobrial IM, Xie W, Padmanabhan S, et al. Phase II trial of weekly bortezomib in combination with rituximab in untreated patients with Waldenstrom macroglobulinemia. *Am J Hematol.* 2010;85:670-674.
32. Dimopoulos MA, Garcia-Sanz R, Gavriatopoulou M, et al. Primary therapy of Waldenstrom macroglobulinemia (WM) with weekly bortezomib, low-dose dexamethasone, and rituximab (BDR): long-term results of a phase 2 study of the European Myeloma Network (EMN). *Blood.* 2013;122:3276-3282.
33. Ghobrial IM, Hong F, Padmanabhan S, et al. Phase II trial of weekly bortezomib in combination with rituximab in relapsed or relapsed and refractory Waldenstrom macroglobulinemia. *J Clin Oncol.* 2010;28:1422-1428.
34. Gertz MA. Waldenstrom macroglobulinemia: 2017 update on diagnosis, risk stratification, and management. *Am J Hematol.* 2017;92:209-217.
35. The NCCN Pediatric Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (Version 1.2021 – September 16, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 6, 2020.
36. The NCCN AIDS-related Kaposi Sarcoma Clinical Practice Guidelines in Oncology (Version 3.2020 – July 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 6, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/14/2020
Selected Revision	The policy was updated to include generics to Velcade approved for intravenous administration.	01/20/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Breyanzi Prior Authorization Policy
- Breyanzi® (lisocabtagene maraleucel suspension for intravenous infusion – Bristol-Myers Squibb)

REVIEW DATE: 02/17/2021; selected revision 03/10/2021

OVERVIEW
Breyanzi, a CD19-directed genetically modified autologous T-cell immunotherapy, is indicated for the treatment of adults with **relapsed or refractory large B-cell lymphoma** after two or more lines of systemic therapy.[1] This includes diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B.

Limitations of use: Breyanzi is not indicated for the treatment of patients with primary central nervous system lymphoma.[1]

Guidelines
The National Comprehensive Cancer Network clinical practice guidelines for B-cell lymphomas (version 2.2021 – February 16, 2021) recommend Breyanzi for the treatment of a variety of lymphomas after at least two prior chemoimmunotherapy regimens.[2,3] This includes relapsed or refractory DLBCL, high-grade B-cell lymphoma, acquired immunodeficiency syndrome (AIDS)-related B-cell lymphoma, post-transplant lymphoproliferative disorders, transformed nodal marginal zone lymphoma and follicular lymphoma, gastric and non-gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and splenic marginal zone lymphoma.[2,3]

Safety
Breyanzi has a Boxed Warning regarding cytokine release syndrome (CRS) and neurologic toxicities.[1] Breyanzi is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Breyanzi REMS.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Breyanzi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Breyanzi as well as the monitoring required for adverse events and long-term efficacy, approval requires Breyanzi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Breyanzi is recommended in those who meet the following criteria:

FDA-Approved Indications

162. B-Cell Lymphoma. Approve a single dose if the patient meets the following criteria (A, B, C, D, E, and F):

A) Patient meets one of the following diagnoses (i, ii, iii, iv, v, vi, vii, viii, ix, x, xi, or xii):
- **i.** Large B-cell lymphoma; OR
- **ii.** Diffuse large B-cell lymphoma; OR
- **iii.** High-grade B-cell lymphoma; OR
- **iv.** Primary mediastinal large B-cell lymphoma; OR
- **v.** Follicular lymphoma; OR
- **vi.** Gastric mucosa-associated lymphoid tissue (MALT) lymphoma; OR
- **vii.** Non-gastric mucosa-associated lymphoid tissue (MALT) lymphoma; OR
- **viii.** Splenic marginal zone lymphoma; OR
- **ix.** Transformed nodal marginal zone lymphoma to diffuse large B-cell lymphoma; OR
- **x.** Transformed follicular lymphoma to diffuse large B-cell lymphoma; OR
- **xi.** Acquired immunodeficiency syndrome (AIDS)-related B-cell lymphoma; OR
- **xii.** Post-transplant lymphoproliferative disorders; AND

B) Patient is ≥ 18 years of age; AND

C) Patient has received two or more lines of systemic therapy; AND

D) Patient has received lymphodepleting chemotherapy prior to infusion of Breyanzi; AND

E) Patient has not been previously treated with CAR-T therapy; AND
Note: CAR-T therapy includes Breyanzi, Kymriah® (tisagenlecleucel suspension for intravenous infusion), Tecartus™ (brexucabtagene suspension for intravenous infusion), and Yescarta® (axicabtagene suspension for intravenous infusion).

F) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Breyanzi is not recommended in the following situations:

171. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

556. Breyanzi® suspension for intravenous infusion [prescribing information]. Bothell, WA: Juno Therapeutics, a Bristol-Myers Squibb company; February 2021.
557. The NCCN B-Cell Lymphoma Clinical Practice Guidelines in Oncology (Version 2.2021 – February 16, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed March 4, 2021.
558. The NCCN Drugs and Biologics Compendium. © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 4, 2021. Search term: lisocabtagene.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	02/17/2021
Selected Revision	**B-Cell Lymphoma:** The following indications were added to the approval criteria: gastric mucosa-associated lymphoid tissue (MALT) lymphoma, non-gastric MALT lymphoma, splenic marginal zone lymphoma, transformed nodal marginal zone lymphoma to diffuse large B-cell lymphoma (DLBCL), transformed follicular lymphoma to DLBCL, acquired immunodeficiency syndrome (AIDS)-related B-cell lymphoma, and post-transplant lymphoproliferative disorders.	03/10/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Cosela Prior Authorization Policy
- Cosela™ (trilaciclib injection for intravenous use – G1 Therapeutics)

REVIEW DATE: 02/24/2021

OVERVIEW

Cosela, a cyclin dependent kinase (CDK) 4/6 kinase inhibitor, is indicated to **decrease the incidence of chemotherapy-induced myelosuppression** in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (SCLC).[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) small cell lung cancer guidelines (version 2.2021 – January 11, 2021) have not addressed Cosela.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cosela. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Cosela as well as the monitoring required for adverse events and long-term efficacy, approval requires Cosela to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cosela is recommended in those who meet the following criteria:

FDA-Approved Indications

23. Small Cell Lung Cancer. Approve for 6 months if the patient meets all of the following criteria (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has extensive-stage disease; AND
- **C)** The medication is used to decrease the incidence of chemotherapy-induced myelosuppression; AND
- **D)** Patient meets ONE of the following criteria (i or ii):
  - **i.** Patient will be receiving platinum (carboplatin or cisplatin) and etoposide-containing chemotherapy regimen; OR
  - **ii.** Patient will be receiving topotecan-containing regimen; AND
- **E)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Cosela is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Cosela™ injection for intravenous use [prescribing information]. Durham, NC: G1 Therapeutics, Inc.; February 2021.
2. The NCCN Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 2.2021 – January 11, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 22, 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	02/24/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Cyramza® (ramucirumab injection for intravenous use – Eli Lilly and Company)

DATE REVIEWED: 06/10/2020

OVERVIEW

Cyramza, a human vascular endothelial growth factor receptor 2 (VEGFR2) antagonist, is approved for the following indications:[1]

1) Gastric or gastroesophageal (GE) junction adenocarcinoma, as a single agent or in combination with paclitaxel injection for the treatment of patients with advanced or metastatic disease with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy;
2) Metastatic non-small cell lung cancer (NSCLC), in combination with docetaxel intravenous injection (Docefrez™, Taxotere®, generics) for the treatment of patients with disease progression on or after platinum-based chemotherapy. Patients with epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Cyramza.
3) Metastatic NSCLC, in combination with erlotinib for the first-line treatment of NSCLC with EGFR exon 19 deletions or exon 21 (L858R) mutations.
4) Metastatic colorectal cancer (mCRC), in combination with FOLFIRI (irinotecan, leucovorin, and 5-fluorouracil [5-FU]) for the treatment of patients with disease progression on or after prior therapy with Avastin® (bevacizumab intravenous injection), oxaliplatin, and a fluoropyrimidine.
5) Hepatocellular carcinoma (HCC), as a single agent in patients who have an alpha fetoprotein of ≥ 400 ng/mL and have been treated with sorafenib.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on colon cancer (version 3.2020 – May 6, 2020) and rectal cancer (version 4.2020 – May 21, 2020) recommend Cyramza as primary therapy and subsequent therapy for patients with unresectable advanced or metastatic disease, and as adjuvant treatment for unresectable metachronous metastases that converted to resectable disease after primary treatment, in combination with either irinotecan or FOLFIRI.[2-4]

The NCCN guidelines on gastric cancer (version 2.2020 – May 13, 2020) and esophageal and esophagogastric junction cancers (version 2.2020 – May 13, 2020) recommend Cyramza as palliative treatment for patients who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease.[4-6]

The NCCN guidelines on NSCLC (version 5.2020 – May 27, 2020) recommend Cyramza as subsequent therapy in combination with docetaxel for metastatic disease for patients who have not previously received docetaxel either following progression on initial cytotoxic therapy or for further progression on a systemic immune checkpoint inhibitor or other systemic therapy.[4,7] Cyramza is also recommended in combination with erlotinib for patients with EGFR mutation positive, recurrent, advanced, or metastatic disease as first-line therapy or as continuation therapy following disease progression on Cyramza and erlotinib.

The NCCN guidelines for hepatobiliary cancers (version 3.2020 – June 1, 2020) recommends Cyramza as a single agent for the treatment of patients with progressive disease with an alpha fetoprotein ≥ 400 ng/mL.[4,8]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Cyramza. All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Cyramza as well as the monitoring required for adverse events and long-term efficacy, approval requires Cyramza to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Cyramza is recommended in those who meet the following criteria:

FDA-Approved Indications

14. **Colon or Rectal Cancer**. Approve for 1 year if the patient meets the following criteria (A, B, and C):
    - **A)** Cyramza is prescribed by or in consultation with an oncologist; AND
    - **B)** The patient has received oxaliplatin and a fluoropyrimidine (e.g., 5-fluorouracil [5-FU], capecitabine); AND
    - **C)** Cyramza will be used in combination with irinotecan or with FOLFIRI (irinotecan, folinic acid [leucovorin], and 5-fluorouracil [5-FU]).

15. **Gastric, Esophagogastric Junction, or Esophageal Cancer**. Approve for 1 year if the patient meets the following criteria (A, B, and C):
    - **A)** Cyramza is prescribed by or in consultation with an oncologist; AND
    - **B)** The patient meets one of the following criteria (i, ii, or iii):
        - **i.** Cyramza will be used alone; OR
        - **ii.** Cyramza will be used in combination with paclitaxel; OR
        - **iii.** Cyramza will be used in combination with fluorouracil and irinotecan; AND
    - **C)** The patient has received chemotherapy with at least ONE of the following (i or ii):
        - **i.** 5-Fluorouracil (5-FU) or capecitabine; OR
        - **ii.** Cisplatin, carboplatin, or oxaliplatin.

16. **Non-Small Cell Lung Cancer.** Approve for 1 year if the patient meets the following criteria (A and B):
    - **A)** Cyramza is prescribed by or in consultation with an oncologist; AND
    - **B)** The patient meets of the following criteria (i or ii):
        - **i.** Cyramza will be used as first-line therapy; AND
            - a) The patient has epidermal growth factor receptor (EGFR) positive disease; AND
            - b) Cyramza will be used in combination with erlotinib (Tarceva®, generics); OR
        - **ii.** Cyramza will be used as subsequent therapy; AND
            - a) Cyramza will be used in combination with docetaxel intravenous injection (Docefrez™, Taxotere®, generics); AND

b) The patient has received targeted drug therapy if the patient's tumor is positive for a targetable mutation (i.e., sensitizing epidermal growth factor receptor mutation, anaplastic lymphoma kinase fusions).

17. Hepatocellular Carcinoma. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Cyramza is prescribed by or in consultation with an oncologist; AND
- **B)** The patient has been treated with Nexavar® (sorafenib tablet); AND
- **C)** Cyramza will be used as a single agent; AND
- **D)** The patient has an alpha fetoprotein of ≥ 400 ng/mL.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Cyramza has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

172. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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336. Cyramza® injection for intravenous use [prescribing information]. Indianapolis, IN: Eli Lilly and Company; June 2020.
337. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 3.2020 – May 6, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 3, 2020.
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342. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 5.2020 – May 27, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 3, 2020.
343. The NCCN Hepatobiliary Cancers Clinical Practice Guidelines in Oncology (Version 3.2020 – June 1, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 3, 2020.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	06/12/2019
Annual Revision	Gastric, Esophagogastric Junction, or Esophageal Cancer: Added criteria for use of Cyramza in combination with fluorouracil and irinotecan. Non-Small Cell Lung Cancer: Added criteria for the use of Cyramza in combination with erlotinib as first-line therapy for patients with EGFR positive disease. Removed criteria for histologic subtypes of NSCLC. Removed Other Cancer Related Indications criteria.	06/10/2020

NSCLC – Non-small cell lung cancer; EGFR – Epidermal growth factor receptor.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Danyelza Prior Authorization Policy
- Danyelza® (naxitamab-gqgk injection – Y-mAbs Therapeutics)

REVIEW DATE: 12/16/2020

OVERVIEW

Danyelza, a glycolipid disialoganglioside (GD2)-binding monoclonal antibody, is indicated, in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), for the treatment of relapsed or refractory high-risk neuroblastoma in the bone or bone marrow in patients ≥ 1 year of age who have demonstrated a partial response, minor response, or stable disease to prior therapy.[1] This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Disease Overview

Neuroblastoma is a rare cancer; however, it is the most common extracranial solid tumor of childhood.[2] Neuroblastoma originates from primodial neural crest cells[3] that develop into sympathetic neural ganglia and adrenal medulla.[2] There are approximately 700 cases diagnosed each year in the US,[4] and around 90% of cases are diagnosed in patients < 5 years of age.[5] Patients most commonly present with an abdominal mass,[4,5] most often arising from the adrenal gland.[2] The mass may be asymptomatic or associated with abdominal pain, hypertension, distension, and constipation. Other tumors may also initiate in the neck, chest, and pelvis.[4] In 10% to 15% of patients, the tumor extends to the epidural or intradural space and may result in spinal cord compression and paraplegia.[2] Patients may

also present with proptosis and periorbital ecchymosis, bone pain, pancytopenia, watery diarrhea, presence of Horner syndrome, and subcutaneous skin nodules.[5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Danyelza. All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Danyelza as well as the monitoring required for adverse events and long-term efficacy, approval requires Danyelza to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Danyelza is recommended in those who meet the following criteria:

FDA-Approved Indications

163. Neuroblastoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 1 year of age; AND
- **B)** Danyelza is used as subsequent therapy; AND
- **C)** Danyelza is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Danyelza is not recommended in the following situations:

173. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

559. Danyelza injection for intravenous use [prescribing information]. New York, NY: Y-mAbs Therapeutics; November 2020.
560. Pastor ER, Mousa SA. Current management of neuroblastoma and future direction. *Crit Rev Oncol Hematol*. 2019;138:38-43.
561. Whittle SB, Smith V, Doherty E, et al. Overview and recent advances in the treatment of neuroblastoma. *Expert Rev Anticancer Ther*. 2017;17:369-386.
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563. PDQ® Pediatric Treatment Editoral Board. PDQ Neuroblastoma Treatment. Bethesda, MD: National Cancer Institute. Updated: June 8, 2020. Available at https://www.cancer.gov/types/neuroblastoma/hp/neuroblastoma-treatment-pdq. Accessed on December 3, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Darzalex Faspro Prior Authorization Policy

- Darzalex™ Faspro (daratumumab and hyaluronidase-fihj injection for subcutaneous use – Janssen Biotech)

OVERVIEW

Darzalex Faspro, a CD38-directed antibody, is approved for use in adults in the following situations:[1]

- **Multiple myeloma**:
  - in newly diagnosed patients, in combination with Revlimid (lenalidomide capsules) and dexamethasone, for the treatment of patients who are ineligible for autologous stem cell transplant and in relapsed/refractory disease, in combination with Revlimid and dexamethasone in patients who have received at least one prior therapy; AND
  - in newly diagnosed patients, in combination with Velcade (bortezumab injection), melphalan, and prednisone in those ineligible for autologous stem cell transplant; AND
  - in newly diagnosed patients, in combination with Velcade, Thalomid (thalidomide capsules), and dexamethasone, for treatment of patients who are eligible for autologous stem cell transplant; AND
  - in patients who have received at least one prior therapy, in combination with Velcade and dexamethasone; AND
  - in patients who have received at least three prior lines of therapy (including a proteasome inhibitor and an immunomodulatory agent or who are double-refractory to a proteasome inhibitor and an immunomodulatory agent), as monotherapy.
- **Light chain (AL) amyloidosis**, in newly diagnosed patients, in combination with Velcade, cyclophosphamide, and dexamethasone.

In multiple myeloma, Darzalex Faspro binds to CD38 and inhibits the growth of CD38-expressing tumor myeloma cells. Darzalex Faspro is a fixed combination of daratumumab and hyaluronidase (recombinant human). It contains the identical molecular antibody of daratumumab available in Darzalex intravenous (IV), but hyaluronidase has been added to facilitate systemic delivery. Darzalex Faspro should be administered under the care of a healthcare provider as a 3 to 5 minute subcutaneous injection. The dose of Darzalex Faspro is fixed regardless of the patient's body surface area (BSA); dose reductions are not recommended. Safety and efficacy is not established in patients < 18 years of age.

Guidelines

Darzalex Faspro is addressed in guidelines from the National Comprehensive Cancer Network (NCCN).

- **Multiple Myeloma:** Guidelines (version 4.2020 – May 8, 2020) address the diagnosis, treatment, and follow-up for patients with multiple myeloma.[2,3] In the most recent update, a footnote was added to clarify that Darzalex Faspro is included in the recommendations for all of the daratumumab-containing regimens. NCCN does recommend Darzalex IV in multiple regimens both as primary treatment and in previously treated disease. Darzalex IV/Velcade/Thalomid/dexamethasone is recommended as primary therapy for transplant candidates. For patients who are non-transplant candidates, Darzalex IV/Revlimid/prednisone is a Preferred regimen, and Darzalex IV/Velcade/melphalan/prednisone is an Other regimen for primary treatment. For previously treated multiple myeloma, Darzalex IV/dexamethasone plus Velcade or Revlimid are among the Preferred regimens, whereas Darzalex IV monotherapy, Darzalex IV/Kyprolis/dexamethasone, and Darzalex IV/Pomalyst/dexamethasone are listed as other recommended regimens.
- **Light Chain Amyloidosis:** NCCN guidelines for systemic light chain amyloidosis have not been updated since approval of Darzalex Faspro in the first line setting. Current guidelines (version 1.2021 – September 1, 2020) list monotherapy with Darzalex Faspro for previously treated disease.[4]

Dosing Information

Darzalex Faspro is available as a single-dose vial containing 1,800 mg of daratumumab and 30,000 units of hyaluronidase per 15 mL. Dosing schedule varies depending on regimen prescribed. Refer to the prescribing information for more specific FDA-approved regimens. Dose reductions are not recommended. In cases of myelosuppression, dose delay may be required to allow recovery of blood cell counts.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Darzalex Faspro. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Darzalex Faspro as well as the monitoring required for adverse events and long-term efficacy, approval requires Darzalex Faspro to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Darzalex Faspro is recommended in those who meet the following criteria:

FDA-Approved Indications

18. Multiple Myeloma. Approve for 1 year if the patient meets BOTH of the following (A and B):
- **21.** The patient meets ONE of the following (i or ii):
  - **A)** Darzalex Faspro is used in combination with at least one other agent.
    Note: Examples of agents that may be used in combination with Darzalex Faspro include Revlimid (lenalidomide capsules), melphalen, or Velcade (bortezumab injection); OR
  - **B)** Patient has tried at least three different regimens for multiple myeloma.
    Note: Examples of agents used in other regimens include Velcade (bortezumab injection), Kyprolis (carfilzomib injection), Revlimid (lenalidomide capsules), cyclophosphamide, Ninlaro (ixazomib capsules); AND
- **22.** Darzalex Faspro is prescribed by or in consultation with an oncologist or a hematologist.

19. Light Chain Amyloidosis. Approve for 1 year if the patient meets all of the following conditions (A, B, and C):
- **A)** Patient meets one of the following (i or ii):
  - **i.** The medication is being used in combination with bortezomib injection, cyclophosphamide, and dexamethasone; OR
  - **ii.** Patient has received at least one other regimen for this condition; AND
    Note: Examples of agents used in other regimens include bortezomib injection, Revlimid (lenalidomide capsules), cyclophosphamide, and melphalan.
- **B)** Patient does NOT have severe heart failure, according to the prescriber; AND
  Note: Severe heart failure is defined as New York Heart Association Class IIIB or IV cardiac disease or Mayo Stage IIIB.
- **C)** The medication is prescribed by or in consultation with an oncologist or a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Darzalex Faspro is not recommended in the following situations:

174. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

37. Darzalex Faspro [prescribing information]. Horsham, PA: Janssen Biotech, Inc.; May 2020.

38. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on April 4,, 2020. Search term: daratumumab, Darzalex Faspro.
39. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (version 3.2020 – March 10, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 18, 2020.
40. The NCCN Systemic light chain amyloidosis Clinical Practice Guidelines in Oncology (version 1.2021 – September 1, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 17, 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	05/06/2020
Update	06/16/2020: Update overview to include updated NCCN guidelines. No criteria changes.	NA
Selected Revision	**Light Chain Amyloidosis:** This newly approved condition was added to the policy. Criteria approve for 1 year if the patient has tried another therapy, or if for a new start, the medication will be given in combination with bortezomib/cyclophosphamide/dexamethasone. For all approvals, the patient does NOT have severe heart failure defined as New York Heart Association Class IIIB or IV cardiac disease, or Mayo Stage IIIB; and Darzalex Faspro must be prescribed by or in consultation with an oncologist or hematologist.	02/03/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Darzalex Intravenous Prior Authorization Policy

- Darzalex™ (daratumumab injection for intravenous use – Janssen Biotech)

REVIEW DATE: 03/10/2021

OVERVIEW

Darzalex, a CD38-directed cytolytic antibody, is indication for treatment of **multiple myeloma** in the following situations:[1]

- in newly diagnosed patients, in combination with Revlimid (lenalidomide capsules) and dexamethasone, for the treatment of patients who are ineligible for autologous stem cell transplant and in relapsed/refractory disease, in combination with Revlimid and dexamethasone in patients who have received at least one prior therapy.
- in newly diagnosed patients, in combination with bortezomib, melphalan, and prednisone in those ineligible for autologous stem cell transplant.
- in newly diagnosed patients, in combination with bortezomib, Thalomid (thalidomide capsules), and dexamethasone, for treatment of patients who are eligible for autologous stem cell transplant.
- in patients who have received at least one prior therapy, in combination with bortezomib and dexamethasone.
- in patients who have received at least two prior therapies (including Revlimid and a proteasome inhibitor), in combination with Pomalyst (pomalidomide capsules) and dexamethasone.
- in patients who have received at least three prior lines of therapy (including a proteasome inhibitor and an immunomodulatory agent or who are double-refractory to a proteasome inhibitor and an immunomodulatory agent), as monotherapy.
- in relapsed/refractory disease, in combination with Kyprolis (carfilzomib intravenous infusion) and dexamethasone in patients who have received one to three prior lines of therapy.

Safety and efficacy is not established in patients < 18 years of age.

Guidelines

Darzalex Intravenous is discussed in guidelines from the National Comprehensive Cancer Network (NCCN).

- **Multiple Myeloma:** NCCN guidelines (version 4.2021 – December 10, 2020) recommend Darzalex in treatment regimens for primary therapy.[2-3] Darzalex/Revlimid/bortezomib/dexamethasone (preferred), Darzalex/bortezomib/ Thalomid/dexamethasone, and Darzalex/cyclophosphamide/bortezomib/dexamethasone are among the recommended regimens for primary therapy for transplant candidates. For patients who are non-transplant candidates, Darzalex/Revlimid/prednisone (preferred), Darzalex/bortezomib/melphalan/prednisone, and Darzalex/cyclophosphamide/bortezomib/dexamethasone are among the regimens for primary treatment. For previously treated multiple myeloma, Darzalex/dexamethasone plus bortezomib, Revlimid, or Kyprolis are among the Preferred regimens, whereas Darzalex monotherapy, Darzalex/Pomalyst/dexamethasone, Darzalex/Xpovio (selinexor tablets)/dexamethasone, and Darzalex/cyclophosphamide/bortezomib/dexamethasone are listed as other or useful in certain circumstances.
- **Systemic Light Chain Amyloidosis:** The NCCN guidelines (version 2.2021 – February 8, 2021) list Darzalex Intravenous as a therapy for previously treated disease, but not for primary therapy.[4] Of note, Darzalex Faspro is indicated and is specifically recommended as a first-line therapy for systemic light chain amyloidosis, given in combination with cyclophosphamide and dexamethasone.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Darzalex. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Darzalex as well as the monitoring required for adverse events and long-term efficacy, approval requires Darzalex to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Darzalex Intravenous is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Multiple Myeloma**. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   1. Patient is ≥ 18 years of age; AND
   2. Patient meets ONE of the following (i or ii):
      - **A)** Darzalex is used in combination with at least one other therapy; OR
        Note: Examples of therapies that may be used in combination with Darzalex include Revlimid (lenalidomide capsules), Pomalyst (pomalidomide capsules), Thalomid (thalidomide capsules), melphalan, bortezomib, or Kyprolis (carfilzomib injection).
      - **B)** Patient has tried at least three different regimens for multiple myeloma; AND
        Note: Examples of agents used in other regimens include bortezomib, Kyprolis (carfilzomib injection), Revlimid (lenalidomide capsules), cyclophosphamide, Ninlaro (ixazomib capsules).
   3. The medication is prescribed by or in consultation with an oncologist or a hematologist.

Other Uses with Supportive Evidence

2. **Light Chain Amyloidosis.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND

B) Patient has received at least one other regimen for this condition; AND
Note: Examples of agents used in other regimens include bortezomib, Revlimid (lenalidomide capsules), cyclophosphamide, and melphalan.
C) The medication is prescribed by or in consultation with an oncologist or a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Darzalex Intravenous is not recommended in the following situations:

175. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Darzalex [prescribing information]. Horsham, PA: Janssen Biotech; August 2020.
2. The NCCN Drugs and Biologics Compendium. © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 5, 2021. Search term: daratumumab.
3. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (Version 4.2021 – December 20, 2021). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 5, 2021.
4. The NCCN Systemic Light Chain Amyloidosis Clinical Practice Guidelines in Oncology (Version 2.2021 –February 8, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 5, 2021.
5. Kaufman GP, Schrier SL, Lafayette RA, et al. Daratumumab yields rapid and deep hematologic responses in patients with heavily pretreated AL amyloidosis. *Blood*. 2017;130(7):900-902.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Multiple Myeloma:** Examples of agents for multiple myeloma were updated in the criteria. **Systemic Light Chain Amyloidosis:** To align with NCCN guidelines, this indication was added an Other Use With Supportive Evidence. Criteria approve if the patient has tried at least one other regimen for this condition, and if prescribed by or in consultation with an oncologist or hematologist.	02/26/2020
Annual Revision	**Multiple Myeloma:** To be consistent with other oncology policies, the requirement that the patient is ≥ 18 years of age was added. **Light Chain Amyloidosis:** To align with this indication in other policies, the qualifier "systemic" was removed from the indication. To align with the multiple myeloma indication, the requirement that the patient is ≥ 18 years of age was added.	03/10/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Decitabine Prior Authorization Policy

- Decitabine injection for intravenous use (Dacogen® – Otsuka America Pharmaceutical, generics)

REVIEW DATE: 10/28/2020

OVERVIEW

Decitabine (Dacogen), a hypomethylating agent, is indicated for the treatment of **myelodysplastic syndromes** (MDS) in adults including previously treated and untreated, *de novo* and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for **Acute Myeloid Leukemia** (version 4.2020 – September 28, 2020) recommend decitabine as a single agent, or in combination with Nexavar® (sorafenib tablet) or Venclexta® (venetoclax tablet) in patients ≥ 60 years of age, and as a single agent, or in combination with Nexavar or Venclaxta for the treatment of relapsed/refractory disease.[2,4] NCCN also recommends decitabine in combination with Venclaxta for relapsed/refractory blastic plasmacytoid dendritic cell neoplasm.

The NCCN guidelines for **Myelodysplastic Syndromes** (version 1.2021 – September 11, 2020) recommend decitabine for the treatment of lower risk and higher risk MDS, and for the treatment of myelodysplastic/myeloproliferative neoplasms.[2,3]

The NCCN guidelines for **Myeloproliferative Neoplasms** (version 1.2020 – May 21, 2020) recommend decitabine for the treatment of myelofibrosis (MF)-accelerated phase or MF-blast/acute myeloid leukemia phase.[2,5]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of decitabine. All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with decitabine as well as the monitoring required for adverse events and long-term efficacy, approval requires decitabine to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of decitabine is recommended in those who meet the following criteria:

FDA-Approved Indications

164. Myelodysplastic Syndromes. Note: Includes Refractory Anemia, Refractory Anemia with Ringed Sideroblasts, Refractory Anemia with Excess Blasts, Refractory Anemia with Excess Blasts in Transformation, Chronic Myelomonocytic Leukemia. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

165. Acute Myeloid Leukemia. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient meets one of the following criteria (i or ii):
  - **i.** Patient is ≥ 60 years of age; OR
  - **ii.** Patient has relapsed or refractory disease; AND
- **B)** The medication is prescribed by or in consultation with an oncologist.

166. Blastic Plasmacytoid Dendritic Cell Neoplasm. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient has relapsed or refractory disease; AND
- **B)** Decitabine is used in combination with Venclexta® (venetoclax tablet); AND
- **C)** The medication is prescribed by or in consultation with an oncologist.

167. Myelofibrosis. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient has accelerate phase, or blast/acute myeloid leukemia phase; AND

B) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of decitabine is not recommended in the following situations:

176. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

564. Dacogen® injection for intravenous use [prescribing information]. Rockville, MD: Otsuka America Pharmaceutical; June 2020.
565. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 12, 2020. Search term: decitabine.
566. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (Version 1.2021 – September 11, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 12, 2020.
567. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (Version 4.2020 – September 28, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 12, 2020.
568. The NCCN Myeloproliferative Neoplasms Clinical Practice Guidelines in Oncology (Version 1.2020 – May 21, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 12, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/16/2019
Annual Revision	No criteria changes.	10/28/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Elzonris Prior Authorization Policy

- Elzonris™ (tagraxofusp-erzs injection for intravenous use – Stemline Therapeutics)

REVIEW DATE: 12/16/2020

OVERVIEW

Elzonris is indicated for the treatment of blastic plasmacytoid dendritic cell neoplasm in patients ≥ 2 years of age.[1]

Elzonris is a CD-123 directed cytotoxin, consisting of recombinant human interleukin-3 (IL-3) fused with truncated diphtheria toxin and is produced by recombinant DNA technology in *Escherichia coli* cells.[1] Elzonris inhibits protein synthesis and causes cell death in cells expressing CD-123.

Guidelines

The National Comprehensive Cancer Network clinical practice guidelines for **acute myeloid leukemia** (version 2.2021 – November 12, 2020) recommend Elzonris as a single agent for the treatment of blastic plasmacytoid dendritic cell neoplasm.[2,3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Elzonris. All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Elzonris as well as the monitoring required for adverse events and long-term efficacy, approval requires Elzonris to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Elzonris is recommended in those who meet the following criteria:

FDA-Approved Indications

168. Blastic Plasmacytoid Dendritic Cell Neoplasm. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient is ≥ 2 years of age; AND

B) Elzonris is prescribed by or consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Elzonris is not recommended in the following situations:

177. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

569. Elzonris™ [prescribing information]. New York, NY: Stemline Therapeutics; December 2018.
570. The NCCN Drugs & Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 8, 2020. Search term: tagraxofusp.
571. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (Version 2.2021 – November 12, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 8, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/03/2019
Annual revision	No criteria changes.	12/11/2019
Annual Revision	No criteria changes.	12/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Empliciti Prior Authorization Policy

- Empliciti® (elotuzumab injection for intravenous use – Bristol-Myers Squibb)

REVIEW DATE: 03/10/2021

OVERVIEW

Empliciti, a SLAMF7 (signaling lymphocytic activation molecule family member 7)-directed immunostimulatory antibody, is indicated in **multiple myeloma**, in the following situations:[1]

0. in patients who have received one to three prior therapies, in combination with Revlimid (lenalidomide capsules) and dexamethasone.
1. in patients who have received at least two prior therapies (including Revlimid and a proteasome inhibitor), in combination with Pomalyst® (pomalidomide) and dexamethasone.

Safety and efficacy have not been established in patients < 18 years of age.

Guidelines

The National Comprehensive Cancer Network (NCCN) Multiple Myeloma clinical practice guidelines (version 4.2021 – December 10, 2020) recommend Empliciti in treatment regimens for patients who were previously treated for multiple myeloma.[3] In this population, Empliciti/Revlimid (lenalidomide capsules)/dexamethasone, Empliciti/Velcade (bortezomib injection)/dexamethasone and Empliciti/Pomalyst/dexamethasone are listed as among the other recommended regimens.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Emplicti. Because of the specialized skills required for evaluation and diagnosis of patients treated with Emplicti as well as the monitoring required for adverse events and long-term efficacy, approval requires Emplicti to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Empliciti is recommended in those who meet one of the following criteria:

FDA-Approved Indications

3. **Multiple Myeloma**. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   4. Patient is ≥ 18 years of age; AND
   5. Patient has tried at least one other regimen for multiple myeloma; AND
      Note: Examples of agents used in other regimens include Velcade (bortezomib injection), Revlimid (lenalidomide capsules), cyclophosphamide, Darzalex (daratumumab injection).
   6. Empliciti is used in combination with at least one other agent; AND
      Note: Examples of agents that may be used in combination with Empliciti include Revlimid® (lenalidomide capsules), Velcade (bortezomib injection), and Pomalyst (pomalidomide capsules).
   7. Empliciti is prescribed by or in consultation with an oncologist or a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Empliciti is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

6. Empliciti® [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; October 19, 2019.
7. The NCCN Drugs and Biologics Compendium. © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 7, 2021. Search term: elotuzumab.
8. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (Version 4.2021 – December 10, 2021). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 7, 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Multiple Myeloma:** Examples of agents were updated in the criteria.	02/26/2020
Annual Revision	**Multiple Myeloma:** To be consistent with other oncology policies, the requirement that the patient is ≥ 18 years of age was added.	03/10/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Enhertu Prior Authorization Policy

- Enhertu® (fam-trastuzumab deruxtecan-nxki injection for intravenous use – Daiichi Sankyo, Inc. and AstraZeneca Pharmaceuticals)

REVIEW DATE: 01/13/2021; selected revision 01/27/2021

OVERVIEW

Enhertu is indicated for the following uses[1]:

- **Breast cancer**, treatment of adult patients with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive disease who have received two or more prior anti-HER2-based regimens in the metastatic setting.[1] This indication is approved under accelerated approval based

on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

- **Gastric cancer**, treatment of adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma, who have received a prior trastuzumab-based regimen.
- Enhertu cannot be substituted for or with trastuzumab or Kadcyla (ado-trastuzumab emtansine).

Guidelines

- **Breast Cancer:** According to the National Comprehensive Cancer Network (NCCN) breast cancer guidelines (version 6.2020 – September 8, 2020), Enhertu is a recommended therapy, as per its FDA-approved indication after two or more prior HER2-targeted therapies, for the treatment of recurrent or Stage IV metastatic disease that is HER2-positive.[2,3] Preferred regimens include trastuzumab + Perjeta + docetaxel (category 1)and trastuzumab + Perjeta + paclitaxel (category 2A). Other recommended regimens include: Kadcyla; trastuzumab + vinorelbine, trastuzumab + capecitabine, Tykerb (lapatinib tablets) + capecitabine, and trastuzumab + Tykerb. For hormone receptor-positive (HR+), HER2-positive disease, endocrine therapy options include aromatase inhibitor ± trastuzumab; aromatase inhibitor + trastuzumab ± Tykerb; fulvestrant ± trastuzamab, tamoxifen ± trastuzumab (all category 2A). For premenopausal patients, ovarian ablation or suppression is recommended in addition to endocrine therapy ± trastuzumab.
- **Colon or Rectal Cancer:** The NCCN Compendium supports use of Enhertu for colon and rectal cancer for patients in the first-line setting who are not candidates for intensive therapy or as subsequent therapy.[2,4,5]
- **Gastric Cancer:** The NCCN guidelines for gastric cancer (version 4.2020 – December 23, 2020) have not addressed Enhertu. Trastuzumab is recommended as a preferred regimen for addition to first-line chemotherapy (fluorouracil or capecitabine + oxaliplatin [category 2A] or cisplatin [category 1]) in HER2 overexpression positive adenocarcinoma
- **Non-Small Cell Lung Cancer (NSCLC):** The NCCN Compendium supports use of Enhertu for HER2-positive disease.[2,6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Enhertu. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Enhertu as well as the monitoring required for adverse events and long-term efficacy, approval requires Enhertu to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Enhertu is recommended in those who meet the following criteria:

FDA-Approved Indications

24. Breast Cancer. Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient has unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive disease; AND

C) Patient has received at least two prior anti-HER2-based regimens in the metastatic setting; AND
Note: Examples of anti-HER2-based regimens include Perjeta (pertuzumab injection for intravenous use) + trastuzumab + docetaxel, Perjeta + trastuzumab + paclitaxel; Kadcyla (ado-trastuzumab emtansine for intravenous use), trastuzumab + capecitabine, trastuzumab + Tykerb (lapatinib tablets).
D) The medication is prescribed by or in consultation with an oncologist.

2. Gastric or Gastroesophageal Junction Cancer. Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
C) Patient has received at least one prior trastuzumab-based regimen; AND
D) The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

3. Colon or Rectal Cancer. Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has human epidermal growth factor receptor 2 (HER2)-positive, *RAS* and *BRAF* wild-type tumors; AND
C) Patient meets ONE of the following (i or ii):
i. Patient has tried at least one chemotherapy; OR
Note: Examples of chemotherapy are fluoropyrimidine such as 5-fluorouracil (5-FU), capecitabine; oxaliplatin, irinotecan, or an adjunctive chemotherapy regimen such as FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).
ii. Patient has unresectable or metastatic disease and is not a candidate for intensive therapy, according to the prescriber; AND
D) The medication is prescribed by or in consultation with an oncologist.

4. Non-Small Cell Lung Cancer (NSCLC). Approve for 1 year if the patient meets ALL of the following criteria (A, B, and C):
A) Patient is ≥ 18 years of age; AND
B) Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
C) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Enhertu is not recommended in the following situations.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

3. Enhertu™ for intravenous use [prescribing information]. Basking Ridge, NJ and Wilmington, DE: Daiichi Sankyo, Inc. and Astrazeneca Pharmaceuticals; January 2021.
4. The NCCN Drugs & Biologics Compendium. © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 10, 2021. Search term: fam-trastuzumab.
5. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 6.2020 – September 8, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 8, 2021.

6. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 1.2021 – December 22, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 10, 2021.
7. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (Version 1.2021 – December 22, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 10, 2021.
8. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 2.2021 – December 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 10, 2021.
9. The NCCN Gastric Cancer Clinical Practice Guidelines in Oncology (Version 4.2020 – December 23, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 20, 2021.

HISTORY

Type of Revision	Summary of Changes*	Review Date
New Policy	New criteria	12/20/2019
Update	2/13/2020; updated with new guidelines. No criteria changes.	--
Annual Revision	**Colon or Rectal Cancer:** Added new approval criteria under Other Uses with Supportive Evidence for use in HER2-positive disease based on guidelines. **Non-Small Cell Lung Cancer:** Added new approval criteria under Other Uses with Supportive Evidence for use in HER2-positive disease based on guidelines.	01/13/2021
Selected Revision	For all indications, added age requirement of ≥ 18 years. **Gastric or Gastroesophageal Junction Cancer:** Added new approval condition and criteria based on FDA-approval.	01/27/2021

HER2 – Human epidermal growth factor receptor 2.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Erbitux Prior Authorization Policy

- Erbitux® (cetuximab injection for intravenous infusion – ImClone LLC/Eli Lilly and Company)

REVIEW DATE: 07/22/2020

OVERVIEW

Erbitux, an epidermal growth factor receptor (EGFR) chimeric monoclonal antibody, is indicated for the treatment of the following conditions:

- **Colorectal cancer** (CRC), *KRAS* wild-type, EGFR-expressing, metastatic CRC as determined by FDA-approved tests for the following uses:
  - In combination with FOLFIRI (irinotecan, 5-fluorouracil [5-FU], leucovorin) for first-line treatment;
  - In combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy; and
  - As a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan.

  Limitation of use: Erbitux is not indicated for treatment of *RAS*-mutant CRC or when the results of the *RAS* mutation tests are unknown.
- **Squamous Cell Carcinoma of the Head and Neck**:
  - In combination with radiation therapy for the initial treatment of locally or regionally advanced SCCHN;
  - In combination with platinum-based therapy with 5-FU for the first-line treatment of patients with recurrent locoregional or metastatic disease; and
  - As a single agent in patients with recurrent or metastatic disease for whom prior platinum-based therapy has failed.[1]

Guidelines

Colon Cancer

The National Comprehensive Cancer Network (NCCN) colon cancer guidelines (version 4.2020 – June 15, 2020) recommend Erbitux as primary therapy for unresectable, advanced, or metastatic *KRAS/NRAS/BRAF* wild-type gene and left-sided tumors only, in combination with irinotecan, FOLFOX (5-FU, leucovorin, oxaliplatin), FOLFIRI, or FOLFOXIRI (5-FU, leucovorin, oxaliplatin, irinotecan) regimens in patients who can tolerate intensive therapy or as a single agent in patients who cannot tolerate intensive therapy.[2,7] Reference to left-sided only disease refers to a primary tumor that originated in the left side of the colon and only refers to use of Erbitux as first-line therapy for metastatic disease. Therapies recommended after first progression vary depending on the initial treatment regimen (i.e., 5-FU/leucovorin-based or capecitabine-based therapy) that was used. The NCCN guidelines recommend Erbitux, in combination with irinotecan, FOLFOX, or FOLFIRI for the subsequent treatment of *KRAS/NRAS/BRAF* wild-type tumors; or in combination with Braftovi (encorafenib capsules) for the subsequent treatment of *BRAF V600E* positive disease. The NCCN rectal cancer guidelines (version 6.2020 – June 25, 2020) make the same recommendations for Erbitux for the treatment of rectal cancer.[3,7]

Head and Neck Cancer
The NCCN head and neck cancers guidelines (version 2.2020 – June 9, 2020) recommend Erbitux in combination with radiation therapy, with a platinum agent (cisplatin or carboplatin) with or without 5-FU, with a platinum agent plus either docetaxel or paclitaxel, or as a single agent.[4,7]

Non-Small Cell Lung Cancer (NSCLC)
The NCCN guidelines on NSCLC (version 6.2020 – June 15, 2020) recommend Erbitux in combination with Gilotrif (afatinib tablets) as subsequent therapy for recurrent, advanced, or metastatic disease in patients with a known sensitizing *EGFR* mutation who are *EGFR T790M* negative, have progressed on EGFR tyrosine kinase inhibitor (TKI) therapy, and have multiple symptomatic systemic lesions; or with a known sensitizing EGFR mutation who have progressed on EGFR TKI therapy, and have asymptomatic disease, symptomatic brain lesions, or isolated symptomatic lesions.[5,7]

In one multicenter, Phase 1b trial conducted in the US and the Netherlands, patients (n = 126) with *EGFR*-mutant lung cancer with acquired resistance to Tarceva or Iressa received oral Gilotrif 40 mg daily plus Erbitux 500 mg/m^2 intravenously every 2 weeks.[6] Patients were heavily pretreated with 52% (n = 65/126) having received ≥ 2 lines of therapy; 79% of patients had received cytotoxic chemotherapy in addition to Tarceva or Iressa. At baseline, the *EGFR* mutation status was as follows: Deletion 19 positive (n = 78), L858R positive (n = 41); and other (n = 4). *T790M* mutation status was available in 124 patients with 71 patients being *T790M* positive and 53 patients being *T790M* negative. The rate of confirmed overall response was 29% (n = 37/126) with all being partial responses; 18% of patient had ≥ 50% tumor shrinkage from baseline. There was no significant difference in overall response rate between patients harboring *T790M*-positive and *T790M*-negative tumors (32% vs. 25%, respectively; P = 0.341). Median duration of response was 5.7 months.

Penile Cancer
The NCCN guidelines on penile cancer (version 1.2020 – January 14, 2020) recommend Erbitux as a single agent for the subsequent treatment of patients with metastatic disease.[7,8]

Squamous Cell Skin Cancer
The NCCN guidelines on squamous cell skin cancer (version 2.2020 – July 14, 2020) recommend Erbitux in combination with radiation therapy for inoperable or incompletely resected regional disease, or as systemic therapy alone in patients ineligible for checkpoint inhibitors with inoperable or incompletely resected regional disease, or regional recurrence or distant metastases.[7,10]

POLICY STATEMENT
Prior authorization is recommended for prescription benefit coverage of Erbitux. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Erbitux as well as the monitoring required for adverse events and long-term efficacy, approval requires Erbitux to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Erbitux is recommended in those who meet the following criteria:

FDA-Approved Indications

4. **Colon and Rectal Cancer.** Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
   8. Patient has advanced or metastatic disease; AND

9. Patient's tumor or metastases are wild-type *RAS* (*KRAS* wild-type and/or *NRAS* wild-type) [that is, the tumor or metastases are *KRAS* and/or *NRAS* mutation negative]; AND
10. If Erbitux is being used for first-line treatment, the primary tumor originated on the left side of the colon (from splenic flexure to rectum); AND
11. Patient meets ONE of the following criteria (i or ii):
- **i.** Patient's tumor or metastases are wild-type *BRAF* (that is, the tumor or metastases are *BRAF V600E* mutation-negative); OR
- **ii.** Patient's tumor or metastases are *BRAF V600E* mutation-positive and the patient meets the following (a and b):
  - **a)** Patient has previously received a chemotherapy regimen for colon or rectal cancer; AND
    Note: Examples of chemotherapy regimens include a fluoropyrimidine such as 5-fluorouracil (5-FU), capecitabine, oxaliplatin, irinotecan, or an adjunctive chemotherapy regimen such as FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).
  - **b)** Erbitux is prescribed in combination with Braftovi (encorafenib capsules); AND

E) Erbitux is prescribed by or in consultation with an oncologist.

5. Head and Neck Squamous Cell Carcinoma (HNSCC). Approve for 1 year if the patient meets the following criteria (A and B):
A) Patient meets ONE of the following criteria (i, ii, or iii):
- **iii.** Erbitux will be used in combination with radiation therapy; OR
- **iv.** Erbitux will be used in combination with platinum-based therapy; OR
  Note: Examples of platinum chemotherapy include cisplatin and carboplatin.
- **v.** Erbitux will be used as a single agent; AND

B) Erbitux is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

6. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
A) Patient has advanced, or metastatic non-small cell lung cancer; AND
B) Patient has a known sensitizing epidermal growth factor receptor *(EGFR)* mutation; AND
C) Patient has received at least ONE tyrosine kinase inhibitor; AND
Note: Examples of tyrosine kinase inhibitors include Tarceva® (erlotinib tablets), Iressa® (gefitinib tablets), or Gilotrif® (afatinib tablets).
D) Erbitux will be used in combination with Gilotrif (afatinib tablets).
E) Erbitux is prescribed by or in consultation with an oncologist.

7. Penile Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
A) Patient has metastatic disease; AND
B) Erbitux will be used as subsequent therapy; AND
C) Erbitux will be used as a single agent; AND
D) Erbitux is prescribed by or in consultation with an oncologist.

8. Squamous Cell Skin Cancer. Approve for 1 year if the patient meets the following criteria (A and B):
A) Patient meets one of the following (i, ii, or iii):
- **i.** Patient has inoperable or incompletely resected regional disease; OR
- **ii.** Patient has regional disease; OR
- **iii.** Patient has distant metastases; AND

B) Erbitux is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Erbitux is not recommended in the following situations:

178. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

9. Erbitux® injection for intravenous infusion [prescribing information]. Indianapolis, IN: Eli Lilly and Company/ImClone LLC; April, 2019.
10. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 4.2020 – June 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed July 16, 2020.
11. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (Version 6.2020 – June 25, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed July 16, 2020.
4. The NCCN Head and Neck Cancer Clinical Practice Guidelines in Oncology (Version 2.2020 – June 9, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 17, 2020.
5. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 6.2020 – June 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 17, 2020.
6. Janjigian YY, Smit EF, Groen HJ, et al. Dual inhibition of EGFR with afatinib and cetuximab in kinase inhibitor-resistant EGFR-mutant lung cancer with and without T790M mutations. *Cancer Discov*. 2014;4:1036-1045.
7. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 15, 2020. Search term: cetuximab.
8. The NCCN Penile Cancer Clinical Practice Guidelines in Oncology (Version 1.2020 – January 14, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 17, 2020.
9. Carthon BC, Ng CS, Pettaway CA, Pagliaro LC. Epidermal growth factor receptor-targeted therapy in locally advanced or metastatic squamous cell carcinoma of the penis. *BJU Int*. 2014;113:871-877.
10. The NCCN Squamous Cell Skin Cancer Clinical Practice Guidelines in Oncology (Version 2.2020 – July 14, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 17, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/24/2019
Annual revision	**Colon and Rectal Cancer.** Revised criteria for *BRAF V600E* criteria to allow Erbitux use in combination with Braftovi only. **Head and Neck Squamous Cell Carcinoma.** Revised criteria for single agent use of Erbitux by removing "in patients who have failed prior platinum-based therapy" and removed the Note. **Non-Small Cell Lung Cancer.** Removed criteria for testing to be negative for epidermal growth factor *T790M* mutation. **Penile Cancer**. Added criteria for penile cancer. **Squamous Cell Skin Cancer.** Added criteria for squamous cell skin cancer.	07/22/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Erwinaze® (asparaginase *Erwinia chrysanthemi* injection for intramuscular and intravenous use – Jazz Pharmaceuticals)

DATE REVIEWED: 06/03/2020

OVERVIEW

Erwinaze is *Erwinia chrysanthemi*-derived L-asparaginase.[1] Asparaginase reduces the plasma levels of asparagine by catalyzing the breakdown of asparagine to aspartic acid and ammonia. Leukemia cells have a deficiency of asparagine synthetase activity and rely on exogenous sources of L-asparagine for survival. Erwinaze depletes plasma L-asparagine levels leading to leukemia cell death.

Erwinaze is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to *Escherichia coli*-derived asparaginase.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for ALL (Version 1.2020 – January 15, 2020) recommend *E. chrysanthemi*-derived asparaginase for patients who have systemic allergic reactions or anaphylaxis due to pegaspargase hypersensitivity, and for induction therapy for ALL in patients ≥ 65 years of age.[2,3]

The NCCN guidelines for Pediatric ALL (Version 2.2020 – November 25, 2019) recommend *E. chrysanthemi*-derived asparaginase for patients who have systemic reactions or anaphylaxis due to pegaspargase hypersensitivity.[3,4]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Erwinaze. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Erwinaze as well as the monitoring required for adverse events and long-term efficacy, approval requires Erwinaze to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Erwinaze is recommended in those who meet the following criteria:

FDA-Approved Indications

169. Acute Lymphoblastic Leukemia. Approve for 1 year if the patient meets the following criteria (A and B):

- **A)** Erwinaze is used for one of the following (i or ii):
  - **i.** The patient has a systemic allergic reaction or anaphylaxis to a pegylated asparaginase product; OR
  - **ii.** Induction therapy in adults ≥ 65 years of age; AND
- **B)** Erwinaze is prescribed by or consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Erwinaze has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

179. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

572. Erwinaze® injection for intramuscular or intravenous use [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals; December 2019.
573. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (Version 1.2020 – January 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 26, 2020.
574. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 26, 2020. Search term: asparaginase Erwinia chrysanthemi.
575. The NCCN Pediatric Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (Version 2.2020 – November 25, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 26, 2020.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	06/05/2019
Annual Revision	No change to criteria	06/03/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Folotyn® (pralatrexate injection – Spectrum Pharmaceuticals)

DATE REVIEWED: 06/03/2020

OVERVIEW

Folotyn is an antineoplastic folate analog which competitively inhibits dihydrofolate reductase.[1]

Folotyn is indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma.[1] This indication is based on overall response rate. Continued approval for this indication may be contingent on verification and description of clinical benefit in a confirmatory trial.

Guidelines

The National Comprehensive Cancer Network (NCCN) Primary Cutaneous Lymphomas clinical practice guidelines (version 2.2020 – April 10, 2020) recommend Folotyn as systemic therapy for mycosis fungoides/Sezary syndrome with or without skin-directed therapy and as a single agent for primary cutaneous CD30+ T-cell lymphoproliferative disorders.[2,3]

The NCCN T-Cell Lymphomas clinical practice guidelines (version 1.2020 – January 6, 2020) recommend Folotyn as a single agent for the second-line or subsequent therapy of relapsed or refractory peripheral T-cell lymphomas including anaplastic large cell lymphoma, peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma; enteropathy-associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, and nodal peripheral T-cell lymphoma with T-follicular helper (TFH) phenotype; follicular T-cell lymphoma; adult T-cell leukemia/lymphoma; extranodal NK/T-cell lymphoma – nasal type; and hepatosplenic gamma-delta T-cell lymphoma.[3,4]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Folotyn. All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Folotyn as well as the monitoring required for adverse events and long-term efficacy, approval requires Folotyn to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Folotyn is recommended in those who meet the following criteria:

FDA-Approved Indications

170. T-Cell Lymphoma, Peripheral. Approve for 1 year if the patient meets the following criteria (A, B, and C):

A) The patient has relapsed or refractory disease; AND

B) Folotyn is used as a single agent; AND

C) Folotyn is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

171. Mycosis Fungoides/Sezary Syndrome. Approve for 1 year if Folotyn is prescribed by or in consultation with an oncologist or dermatologist.

172. Cutaneous CD30+ T-Cell Lymphoproliferative Disorders. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** The patient has one of the following diagnoses (i or ii):
  - **i.** Primary cutaneous anaplastic large cell lymphoma with multifocal lesions; OR
  - **ii.** Cutaneous anaplastic large cell lymphoma with regional nodes; AND
- **B)** Folotyn is used as a single agent; AND
- **C)** Folotyn is prescribed by or in consultation with an oncologist.

173. Adult T-Cell Leukemia/Lymphoma, Acute or Lymphoma Subtype. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Folotyn is used as second-line or subsequent therapy; AND
- **B)** Folotyn is used as a single agent; AND
- **C)** Folotyn is prescribed by or in consultation with an oncologist.

174. Extranodal NK/T-Cell Lymphoma, Nasal Type. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** The patient has relapsed/refractory disease following combination, asparaginase-based chemotherapy; AND
- **B)** Folotyn is used as a single agent; AND
- **C)** Folotyn is prescribed by or in consultation with an oncologist.

175. Hepatosplenic Gamma-Delta T-Cell Lymphoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Folotyn is used as second-line or subsequent therapy; AND
- **B)** Folotyn is used as a single agent; AND
- **C)** Folotyn is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Folotyn has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

180. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

576. Folotyn® injection [prescribing information]. East Windsor, NJ: Acrotech Biopharma; May 2020.
577. The NCCN Primary Cutaneous Lymphomas Clinical Practice Guidelines in Oncology (Version 2.2020 – April 10, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 26, 2020.

578. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 26, 2020. Search term: pralatrexate.
579. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 1.2020 – January 6, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 26, 2020.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	06/05/2019
Annual Revision	Cutaneous CD30+ T-Cell Lymphoproliferative Disorders: added "primary' to cutaneous anaplastic large cell lymphoma. Hepatosplenic Gamma-Delta T-Cell Lymphoma: added use as "second-line" therapy to criteria and removed "after two primary treatment regimens" from the criteria.	06/03/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Fulvestrant (Faslodex injection for intramuscular use – AstraZeneca; generics)

DATE REVIEWED: 05/06/2020

OVERVIEW

Fulvestrant is an estrogen receptor (ER) antagonist that binds to the estrogen receptor in a competitive manner.[1] Its affinity to the ER is comparable to that of estradiol. By binding to the ER, Faslodex downregulates the ER protein in human breast cancer cells.

Fulvestrant is indicated for the following:

- As monotherapy, for the treatment of hormone receptor-positive (HR+) [i.e., ER+ or progesterone receptor (PR+)], human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy; or
- As monotherapy, for the treatment of patients with HR+ advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.[1]
- Fulvestrant is indicated in combination with Kisqali (ribociclib tablets) as initial endocrine based therapy or following disease progression on endocrine therapy for HR+, HER2-negative advanced or metastatic breast cancer in postmenopausal women.
- Fulvestrant is indicated in combination with Ibrance® (palbociclib capsules) or Verzenio™ (abemaciclib tablets) in women with disease progression after endocrine therapy for HR+, HER2-negative advanced or metastatic breast cancer.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on breast cancer (version 3.2020 – March 6, 2020) recommends fulvestrant in combination with cyclin dependent kinase 4/6 inhibitors (i.e., Ibrance, Kisqali, Verzenio) and non-steroidal aromatase inhibitors (i.e., anastrozole, letrozole) for the treatment of recurrent or metastatic HR+, HER2-negative disease (category 1 preferred regimen).[2] The guidelines note that CDK4/6 inhibitors or anastrozole/letrozole in combination with fulvestrant may be considered as a treatment option for first-line therapy for women who are postmenopausal or premenopausal (receiving ovarian suppression or ablation). If CDK4/6 inhibitor was not previously used, fulvestrant + CDK4/6 inhibitor is a category 1, preferred regimen as second/subsequent-line therapy. It is also recommended as a second/subsequent-line therapy, category 1, preferred regimen for *PIK3CA* mutated tumors in combination with Piqray (alpelisib tablets). Fulvestrant in combination with everolimus (category 2A) is another option for second/subsequent-line therapy. As monotherapy, fulvestrant is listed

as one of the preferred options (category 2A) for second/subsequent-line therapy. Men with breast cancer should be treated similarly to postmenopausal women, except that use of an aromatase inhibitor is ineffective without concomitant suppression of testicular steroidogenesis.[2-3] Based on a review article, there are limited data to support the use of fulvestrant monotherapy in men; however, there are no randomized prospective or retrospective trial data with the use of everolimus or cyclin dependent kinase (CDK) 4/6 inhibitor in men.[4]

The NCCN compendium for fulvestrant and the respective guidelines support fulvestrant use for low-grade serous carcinoma (ovarian/fallopian tube/primary peritoneal cancer), uterine sarcoma, and endometrial carcinoma.[3]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of fulvestrant. All approvals are provided for the duration noted below. Because of the of the specialized skills required for evaluation and diagnosis of patients treated with fulvestrant, as well as the monitoring required for adverse events and long-term efficacy, approval requires fulvestrant to be prescribed by or in consultation with a physician who specializes in the condition being treated.

In the approval indication, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: men/males are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression. Female/women are defined as individuals with the biological traits of a woman, regardless of the individual's gender identity or gender expression.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of fulvestrant is recommended in those who meet one of the following criteria:

FDA-Approved Indications

9. **Breast Cancer – Fulvestrant Monotherapy**. Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **12.** The medication is prescribed by or in consultation with an oncologist; AND
   - **13.** Patient has recurrent or metastatic hormone receptor (HR)-positive (i.e., estrogen receptor- [ER] or progesterone receptor [PR]-positive) disease; AND
   - **14.** Patient meets one of the following criteria (i or ii):
     - **i.** Patient is a postmenopausal female* or a male*; OR
     - **ii.** Patient is premenopausal and is receiving ovarian suppression with a gonadotropin-releasing hormone (GnRH) agonist or has had ovarian ablation.
       Note: Examples of GnRH agonist are Zoladex (goserelin), Lupron (leuprolide), Trelstar (triptorelin). Examples of ovarian ablation are surgical bilateral oophorectomy, ovarian irradiation.

   * Refer to the Policy Statement.

10. **Breast Cancer – Fulvestrant Combination Therapy**. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
    - **I)** The medication is prescribed by or in consultation with an oncologist; AND
    - **J)** Patient has recurrent or metastatic hormone receptor (HR)-positive (i.e., estrogen receptor- [ER] or progesterone receptor [PR]-positive) disease; AND
    - **K)** Patient meets ONE of the following criteria (i or ii):
      - **A)** Patient is a postmenopausal female* or a male*; OR

ii. Patient is premenopausal and is receiving ovarian suppression with a gonadotropin- releasing hormone (GnRH) agonist or has had ovarian ablation.
Note: Examples of GnRH agonist are Zoladex (goserelin), Lupron (leuprolide), Trelstar (triptorelin). Examples of ovarian ablation are surgical bilateral oophorectomy, ovarian irradiation; AND

L) Patient meets one of the following criteria (i or ii):
i. Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer and meets one of the following criteria (a or b):
a) The patient meets both of the following criteria (1 and 2):
(1) The patient has progressed on or after at least one prior endocrine-based therapy.
Note: Examples of endocrine therapy are tamoxifen, anastrozole, letrozole, exemestane; AND
(2) The patient has *PIK3CA*-mutated tumor and the medication is used in combination with Piqray (alpelisib tablets); OR
b) The medication will be used in combination with one of: a cyclin dependent kinase 4/6 (CDK 4/6) inhibitor, non-steroidal aromatase inhibitor (i.e., anastrozole or letrozole), or everolimus.
Note: Examples of CDK4/6 inhibitors are Kisqali (ribociclib tablets), Ibrance (palbociclib capsules), Verzenio (abemaciclib tablets); OR
ii. Patient has human epidermal growth factor receptor 2 (HER2)-positive breast cancer and the medication is used in combination with trastuzumab products.

* Refer to the Policy Statement.

Other Uses with Supportive Evidence

11. Ovarian/Fallopian Tube/Primary Peritoneal Cancer. Approve for 1 year if the patient meets the following criteria (A and B):
A) The medication is prescribed by or in consultation with an oncologist; AND
B) The medication is used as recurrence therapy for low-grade serous carcinoma.

12. Uterine Sarcoma. Approve for 1 year if the patient meets the following criteria (A and B):
A) The medication is prescribed by or in consultation with an oncologist; AND
B) Patient meets one of the following criteria (i or ii):
i. Patient has low-grade endometrial stromal sarcoma; OR
ii. Patient has hormone receptor-positive uterine leiomyosarcoma.

13. Endometrial Carcinoma. Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Fulvestrant has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

2. Other Indications (Non-Cancer). Coverage is not recommended for circumstances not listed in the Authorization Criteria (FDA-approved indications and Other Uses with Supportive Evidence). Criteria will be updated as new published data are available.

REFERENCES

12. Faslodex® injection for intramuscular use [prescribing information]. Wilmington, DE: AstraZeneca; March 2019.
13. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 3.2020 – March 6, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 4, 2020.
14. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 4, 2020. Search term: fulvestrant.

HISTORY

Type of Revision	Summary of Changes*	Date Reviewed
New policy	New criteria	04/10/2019
Selected revision	Due to the availability of generics, changed policy name to Oncology – Fulvestrant instead of brand name. For Breast Cancer – Fulvestrant Combination Therapy, added criteria for combination use with Piqray if patient has tried prior endocrine regimen. Based on guidelines, fulvestrant and CDK4/6 inhibitor/Afinitor use does not require prior endocrine regimen. Due to generics, changed reference from brand name to generic name where applicable.	10/02/2019
Annual revision	For Breast Cancer - Fulvestrant Combination Therapy indication, added non-steroidal aromatase inhibitors (i.e., letrozole or anastrozole) as one of the agents that could be used in combination with fulvestrant.	05/06/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Gazyva Prior Authorization Policy

- Gazyva® (obinutuzumab injection for intravenous use – Genentech, Inc.)

REVIEW DATE: 10/14/2020

OVERVIEW

Gazyva is indicated for the treatment of:

- **Chronic lymphocytic leukemia**, in combination with chlorambucil in previously untreated patients.
- **Follicular lymphoma**, in combination with bendamustine followed by Gazyva monotherapy, for patients who relapse or are refractory to a rituximab containing regimen.
- **Follicular lymphoma, stage II bulky, III or IV**, in combination with chemotherapy, followed by Gazyva monotherapy for patients achieving at least a partial remission, in previously untreated patients.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on **B-cell lymphomas** (version 4.2020 – August 13, 2020) recommend Gazyva for the first-line and second-line treatment of follicular lymphoma (grade 1 or 2) in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CVP (cyclophosphamide, vincristine, and prednisone), bendamustine, or Revlimid (lenalidomide capsules); or as maintenance treatment.[2,4] The guidelines also recommend Gazyva as second-line or maintenance therapy for gastric and nongastric MALT lymphoma, nodal marginal zone lymphoma, and splenic marginal zone lymphoma. Gazyva is also recommended as a substitute for rituximab products (e.g., Rituxan, Truxima) in patients experiencing rare complications, regardless of histology.

The NCCN guidelines on c**hronic lymphocytic leukemia/small lymphocytic lymphoma** (CLL/SLL) (version 1.2021 – September 28, 2020) recommends Gazyva in combination with Calquence® (acalabrutinib capsules); in combination with Venclexta® (venetoclax tablets) in frail patients with significant comorbidities; in combination with chlorambucil, bendamustine, Venclexta, or Imbruvica® (ibrutinib capsules and tablets); or as a single agent for the first-line treatment of CLL/SLL without del(17p)/TP53 mutation.[2,3] Gazyva is also recommended as a single agent or

in combination with Venclexta or Calquence for the first-line treatment of CLL/SLL with del(17p)/TP53 mutation; and as a single agent for relapsed or refractory CLL/SLL without del(17p)/TP53 mutation.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Gazyva. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Gazyva as well as the monitoring required for adverse events and long-term efficacy, approval requires Gazyva to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Gazyva is recommended in those who meet the following criteria:

FDA-Approved Indications

176. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Approve for 6 months if the patient meets the following criteria (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The medication is prescribed by or in consultation with an oncologist.

177. Follicular Lymphoma. Approve for 6 months if the patient meets the following criteria (A, B, and C):
- **B)** Patient is ≥ 18 years of age; AND
- **C)** Gazyva will be used in ONE of the following situations (i, ii, or iii):
  - **i.** In combination with chemotherapy; OR
    Note: Examples include CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CVP (cyclophosphamide, vincristine, and prednisone), or bendamustine.
  - **ii.** For maintenance treatment following Gazyva in combination with chemotherapy; OR
  - **iii.** Patient experienced an adverse event or intolerance to a rituximab product; AND
    Note: Examples of adverse events or intolerance includes paraneoplastic pemphigus, Stevens-Johnson syndrome, Lichenoid Dermatitis, vesiculobullous dermatitis, toxic epidermal necrolysis.[2,4]
- **C)** The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

178. Marginal Zone Lymphoma. Note: Includes Nodal Marginal Zone Lymphoma, Splenic Marginal Zone Lymphoma, Gastric MALT, or Nongastric MALT. Approve for 6 months if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Gazyva will be used in ONE of the following situations (i or ii):
  - **i.** Second-line or subsequent therapy for recurrent or progressive disease; OR
  - **ii.** Patient experienced an adverse event or intolerance to a rituximab product: AND
    Note: Examples of adverse events or intolerance includes paraneoplastic pemphigus, Stevens-Johnson syndrome, Lichenoid Dermatitis, vesiculobullous dermatitis, toxic epidermal necrolysis.[2,4]
- **C)** The medication is prescribed by or in consultation with an oncologist.

179. Other B-Cell Lymphoma. Note: Includes Diffuse Large B-Cell Lymphoma, Mantle Cell Lymphoma, High-Grade B-Cell Lymphoma, Burkitt Lymphoma, AIDS-Related B-Cell Lymphoma,

Post-Transplant Lymphoproliferative Disorders, Castleman's Disease. Approve for 6 months if the patient meets the following criteria (A, B, and C):

A) Patient is ≥ 18 years of age; AND

B) Patient experienced an adverse event or intolerance to a rituximab product: AND
Note: Includes paraneoplastic pemphigus, Stevens-Johnson syndrome, Lichenoid Dermatitis, vesiculobullous dermatitis, toxic epidermal necrolysis.[2,4]

C) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Gazyva is not recommended in the following situations:

181. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

580. Gazyva® [prescribing information]. South San Francisco, CA: Genentech, Inc.; March 2020.
581. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 1, 2020. Search term: obinutuzumab.
582. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (Version 1.2021 – September 28, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 1, 2020.
583. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 4.2020 – August 13, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 1, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/09/2019
Annual Revision	No criteria changes.	10/14/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Gonadotropin-Releasing Hormone Analogs Prior Authorization Policy

- Eligard® (leuprolide acetate for subcutaneous injection – Tolmar Pharmaceuticals Inc.)
- Firmagon® (degarelix for subcutaneous injection – Ferring Pharmaceuticals Inc.)
- Trelstar® (triptorelin pamoate for intramuscular injection – Verity Pharmaceuticals Inc.)

REVIEW DATE: 12/09/2020

OVERVIEW

Eligard, Trelstar, and Firmagon are all indicated for the treatment of advanced prostate cancer.[1-3] Eligard and Trelstar are gonadotropin-releasing hormone (GnRH) agonists, whereas Firmagon is a GnRH antagonist. Both Eligard and Firmagon are as a subcutaneous injection and Trelstar is administered as an intramuscular injection.

Guidelines

The National Comprehensive Cancer Network (NCCN) Guidelines for Head and Neck Cancer (version 1.2021 – November 9, 2020) recommend the use of androgen receptor therapy (i.e., leuprolide, bicalutamide) for androgen receptor (AR)-positive, recurrent salivary gland tumors with distant metastases.[4,5]

The NCCN Guidelines for Prostate Cancer (version 3.2020 – November 17, 2020) note androgen deprivation therapy as primary systemic therapy for regional or advanced prostate cancer and as neoadjuvant/concomitant/adjuvant therapy in combination with radiation in localized or locally advanced prostate cancer.[6] Many different drugs can be used as androgen deprivation therapy, including Eligard, Firmagon, and Trelstar.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Eligard, Firmagon, and Trelstar. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Eligard, Firmagon, and Trelstar as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Eligard, Firmagon, or Trelstar is recommended in those who meet the following criteria:

FDA-Approved Indications

180. Prostate Cancer. Approve Eligard, Firmagon, or Trelstar for 1 year if prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

181. Head and Neck Cancer – Salivary Gland Tumors. Approve Eligard for 1 year if the patient meets the following criteria (A, B, and C):

A) Patient has recurrent disease with distant metastases; AND
B) Patient has androgen receptor (AR)-positive disease; AND
C) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Eligard, Trelstar, or Firmagon is not recommended in the following situations:

182. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

584. Eligard® Subcutaneous Injection [prescribing information]. Fort Collins, CO: Tolmar Pharmaceuticals Inc.; April 2019.
585. Firmagon® Subcutaneous Injection [prescribing information]. Parsippany, NJ: Ferring Pharmaceuticals Inc.; February 2020.
586. Trelstar® Intramuscular Injection [prescribing information]. Wayne, PA: Verity Pharmaceuticals, Inc; May 2020.
587. The NCCN Head and Neck Cancer Clinical Practice Guidelines in Oncology (Version 1.2021 – November 9, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 24, 2020.
588. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on November 24, 2020. Search terms: leuprolide acetate, degarelix, triptorelin pamoate.
589. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (Version 3.2020 – November 17, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on November 24, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	11/28/2018

Annual Revision	No criteria changes.	12/04/2019
Update	09/22/2020: Revised policy name from "Oncology (Injectable) – Gonadotropin-Releasing Hormone Analogs (Eligard, Firmagon, Trelstar) PA Policy" to "Oncology (Injectable) – Gonadotropin-Releasing Hormone Analogs PA Policy".	NA
Annual Revision	No criteria changes.	12/09/2020

NA – Not applicable.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Halaven® (eribulin mesylate injection for intravenous use – Eisai Inc.)

DATE REVIEWED: 02/26/2020

OVERVIEW

Halaven is a microtubule inhibitor indicated for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease.[1] Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting. Halaven is also indicated for the treatment of patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen.

Guidelines

The National Comprehensive Cancer Network (NCCN) breast cancer guidelines (version 2.2020 – February 5, 2020) lists Halaven as one of the preferred single-agent regimens for patients with human epidermal growth factor receptor-2 (HER2)-negative recurrent or metastatic breast cancer.[2,3] It can also be used in HER2-positive disease when used in combination with Herceptin (trastuzumab for intravenous use) for recurrent or metastatic disease.

The NCCN soft tissue sarcoma guidelines (version 6.2019 – February 10, 2020) lists Halaven as a single-agent therapy (most are category 2A) for a variety of subtypes with non-specific histologies.[3] For liposarcoma, Halaven is a category 1 recommended agent. The NCCN compendium[2] recommends Halaven for the following soft tissue sarcoma subtypes: extremity/superficial trunk, head/neck, retroperitoneal/intra-abdominal, angiosarcoma, and pleomorphic rhabdomyosarcoma. Halaven is a category 2B recommended therapy for uterine sarcoma.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Halaven. Because of the specialized skills required for evaluation and diagnosis of patients treated with Halaven as well as the monitoring required for adverse events and long-term efficacy, approval requires the medication to be prescribed by or in consultation with a prescriber who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Halaven is recommended in those who meet the following criteria:

FDA-Approved Indications

3. Breast Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):

A) The patient has metastatic disease; AND
B) The patient has been previously treated with at least two chemotherapy regimens.
Note: Examples of chemotherapy include doxorubicin, epirubicin, paclitaxel, docetaxel, Abraxane (albumin-bound paclitaxel); AND
C) The medication is prescribed by or in consultation with an oncologist.

2. Soft Tissue Sarcoma of the Extremity/Superficial Trunk, Head/Neck, Retroperitoneal/Intra-Abdominal, Angiosarcoma, Pleomorphic Rhabdomyosarcoma, and Liposarcoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
A) The patient has unresectable, progressive, or metastatic disease; AND
B) The patient has been treated with at least one prior anthracycline-containing chemotherapy regimen.
Note: Examples of chemotherapy regimen include doxorubicin and dacarbazine, doxorubicin with ifosfamide and mesna, epirubicin with ifosfamide and mesna; AND
C) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Halaven has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

272. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

428. Halaven® Intravenous Infusion [prescribing information]. Woodcliff Lake, NJ: Eisai Inc.; October 2016
429. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 18, 2020. Search term: eribulin mesylate.
430. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 2.2020 – February 5, 2020). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 18, 2020.
431. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (Version 6.2019 – February 10, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 18, 2020.

HISTORY

Type of Revision	Summary of Changes*	Date Reviewed
New Policy	New criteria	09/11/2019
Early annual revision	No criteria changes	02/26/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Herceptin Hylecta Prior Authorization Policy
- Herceptin Hylecta™ (trastuzumab and hyaluronidase-oysk for subcutaneous use – Genentech)

REVIEW DATE: 03/17/2021

OVERVIEW

Herceptin Hylecta is indicated for the following uses:[1]

- **Breast Cancer, adjuvant treatment** of adults with human epidermal growth factor receptor 2 (HER2) overexpressing node positive or node negative (estrogen receptor [ER]-/progesterone receptor [PR]-negative or with one high risk feature) breast cancer:
  - **a)** As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel.
  - **b)** As part of a treatment regimen with docetaxel and carboplatin.
  - **c)** As a single agent following multi-modality anthracycline based therapy.
- **Breast Cancer**, metastatic, in adults with HER2-overexpressing disease:
  - **a)** In combination with paclitaxel for first-line treatment.
  - **b)** As a single agent for the treatment of patients who have received one or more chemotherapy regimens for metastatic disease.

Guidelines

The National Comprehensive Cancer Network (NCCN) Breast Cancer clinical practice guidelines (version 2.2021 – March 12, 2021) recommend substitution of Herceptin Hylecta for trastuzumab intravenous (IV) in the treatment algorithm.[2,3] The guidelines note the different dose and dosage form of Herceptin Hylecta compared with trastuzumab. It is also noted that Herceptin Hylecta cannot be substituted for Kadcyla™ (ado-trastuzumab emtansine for intravenous injection). Trastuzumab is recommended as part of a preferred regimen in the preoperative/adjuvant therapy setting in HER2-positive disease. As part of a preferred regimen, it can be used in combination with doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab ± Perjeta® (pertuzumab for injection); paclitaxel + trastuzumab; and docetaxel/carboplatin/trastuzumab ± Perjeta. Docetaxel + cyclophosphamide + trastuzumab is noted under "useful in certain circumstances." Other recommended regimens are doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab ± Perjeta. If there is no residual disease after preoperative therapy or no preoperative therapy: complete up to one year of HER2-targeted therapy with trastuzumab (category 1) ± Perjeta. If there is residual disease after preoperative therapy: Kadcyla alone (category 1) is preferred. If Kadcyla is discontinued for toxicity, then trastuzumab (category 1) ± Perjeta can be used to complete 1 year of therapy. For systemic treatment of recurrent or stage IV (M1) disease that is hormone-receptor positive and HER2-positive, trastuzumab + Perjeta + taxane is preferred; or trastuzumab + chemotherapy; or Kadcyla can be used; or endocrine therapy ± HER2-targeted therapy. For HER2-positive disease and postmenopausal and premenopausal patients endocrine therapy options include, aromatase inhibitor ± trastuzumab; aromatase inhibitor + trastuzumab ± Tykerb® (lapatinib tablets); Faslodex® (fulvestrant for injection) ± trastuzamab, tamoxifen ± trastuzumab (all category 2A). For premenopausal patients, ovarian ablation or suppression is recommended in addition to endocrine therapy ± trastuzumab.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Herceptin Hylecta. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Herceptin Hylecta as well as the monitoring required for adverse events and long-term efficacy, approval requires Herceptin Hylecta to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Herceptin Hylecta is recommended in those who meet the following criteria:

FDA-Approved Indications

25. Breast Cancer. Approve for the duration noted below if the patient meets ALL of the criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
- **C)** Patient meets one of the following criteria (i or ii):
  - **i.** Approve for up to 1 year (total) if the medication is used for adjuvant treatment; OR
  - **ii.** Approve for 1 year if the medication is used for metastatic disease; AND
- **D)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Herceptin Hylecta is not recommended in the following situations:

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

10. Herceptin Hylecta™ for subcutaneous use [prescribing information]. South San Francisco, CA: Genentech, Inc.; February 2019.
11. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 2.2021 – March 12, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 15, 2021.
12. The NCCN Drugs and Biologics Compendium. © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 15, 2021. Search term: trastuzumab hyaluronidase.

HISTORY

Type of Revision	Summary of Changes	Review Date
New policy	New criteria	03/20/2019
Update	03/31/2019: For clarity, in the Breast Cancer indication added "for the duration noted below" to look for different approval durations. Also, deleted "Breast Cancer – Adjuvant Treatment for Greater than 1 year" from Conditions Not Recommended for Approval, since this is already being addressed with the limited approval duration within criteria.	--
Annual Revision	No criteria changes	03/25/2020
Annual Revision	**Breast Cancer:** Added age criterion for approval	03/17/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Imfinzi Prior Authorization Policy
- Imfinzi® (durvalumab injection for intravenous use – AstraZeneca)

REVIEW DATE: 07/15/2020; 03/03/2021 selected revision

OVERVIEW

Imfinzi, a programmed cell death ligand 1 (PD-L1) blocking antibody, is indicated for the treatment of the following conditions:

- **Non-small cell lung cancer (NSCLC)**, in adult patients with unresectable Stage III disease that has not progressed following concurrent platinum-based chemotherapy and radiation therapy.
- **Small cell lung cancer**, in combination with etoposide and either carboplatin or cisplatin for the first-line treatment of adult patients with extensive-stage disease.

Guidelines

- **Non-Small Cell Lung Cancer:** The National Comprehensive Cancer Network (NCCN) guidelines on NSCLC (version 6.2020 – June 15, 2020) recommends Imfinzi (category 1) as consolidation therapy for patients with unresectable Stage III disease with a performance status of 0 or 1.[3,4] Imfinzi can be used regardless of the PD-L1 status in patients who have not progressed after two or more cycles of definitive concurrent platinum-based chemoradiation therapy. Imfinzi is not recommended for patients following definitive surgical resection.
- **Small Cell Lung Cancer:** The NCCN guidelines for small cell lung cancer (version 4.2020 – July 7, 2020) recommends the use of Imfinzi in combination with etoposide and carboplatin/cisplatin as "preferred" first-line treatment option (category 1).[3,5] Imfinzi is used in maintenance setting, after 4 cycles in combination with chemotherapy, as single-agent once every 28 days until disease progression or unacceptable toxicity.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Imfinzi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Imfinzi, as well as the monitoring required for adverse events and long-term efficacy, approval requires Imfinzi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Imfinzi is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Non-Small Cell Lung Cancer.** Approve for 1 year (total) of therapy if the patient meets the following criteria (A, B, and C):
   - **A)** Patient has unresectable Stage III disease; AND
   - **B)** Patient has not had disease progression following treatment with concurrent platinum-based chemotherapy and radiation therapy; AND
   - **C)** The medication is prescribed by or in consultation with an oncologist.

2. **Small Cell Lung Cancer.** Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient meets one of the following (i or ii):
     - **i.** The medication is used in combination with etoposide and platinum chemotherapy (cisplatin or carboplatin); OR
     - **ii.** The medication is used as single-agent for maintenance after chemotherapy; AND
   - **B)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Imfinzi is not recommended in the following situations:

273. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

15. Imfinzi® injection for intravenous use [prescribing information]. Wilmington, DE: AstraZeneca; February 2021.
16. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 10, 2020. Search term: durvalumab.
17. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 6.2020 – June 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed July 10, 2020.
18. The NCCN Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 4.2020 – July 7, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed July 10, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	06/18/2019
Annual Revision	Added new FDA-approved indication for small cell lung cancer. Changed "Imfinzi" to "The medication" in reference to prescriber.	07/15/2020
Selected Revision	• **Urothelial Carcinoma:** Deleted approval condition and criteria based on FDA withdrawal of approval indication. The confirmatory trial did not meet the primary efficacy endpoints.	03/03/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Imlygic® (talimogene laherparepvec intralesional injection – Amgen)

TAC APPROVAL DATE: 02/19/2020

OVERVIEW

Imlygic is an oncolytic viral therapy indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.[1] It is a limitation of use that Imlygic has not been shown

to improve overall survival or have an effect on visceral metastases. Imlygic should be continued for at least 6 months, unless other treatment is required or there are no injectable lesions to treat and may also be reinitiated if new unresectable cutaneous, subcutaneous, or nodal lesions appear following a complete response. In the pivotal trial, adults with unresectable stage III (30%) or stage IV (70%) melanoma were treated for at least 6 months, or until no remaining injectable lesions. During the initial 6 months of the trial, treatment continued despite increased size or number of lesions. Following 6 months of treatment, patients could continue Imlygic until clinically relevant disease progression (i.e., disease progression associated with a decline in performance status and/or alternative therapy was needed, according to the prescriber). Imlygic requires specialized storage conditions (-130° to -94° F). Personal protective equipment (including a gown/laboratory coat, safety glasses or face shield, and gloves) while preparing or administering, and procedures for accidental exposure to Imlygic should be followed. Healthcare providers should be prepared to manage adverse events, including immune-mediated events (e.g., glomerulonephritis, vasculitis, pneumonitis) and plasmocytoma at the injection site. Safety and efficacy have not been established in patients < 18 years of age.

Disease Overview

Oncolytic virus immunotherapy is a form of cancer therapy which uses native or genetically modified viruses to selectively enter, replicate, and lyse tumor cells.[2] Oncolytic viruses are able to be engineered to deliver therapeutic genes to cancer cells, thus, causing additional antitumor effects through cytokine secretion and induction of antitumor immune response.[3] Of note, herpes simplex virus (HSV)-1 is an attractive option for oncolytic virus therapy because it can infect a wide range of host cells and causes lysis following viral replication.[2] Imlygic, previously referred to as T-VEC, is the first oncolytic virus immunotherapy approved in the US. It is genetically modified to attenuate HSV-1, increase selectivity for cancer cells, and secrete granulocyte macrophage colony-stimulating factor (GM-CSF). Secretion of GM-CSF is intended to enhance tumor antigen presentation to the immune system and induce systemic immune responses to the tumors.[3]

Clinical Efficacy

In the pivotal trial, the initial dose of Imlygic was administered at 10^6 PFU/mL (to seroconvert HSV-seronegative patients). Subsequent doses were 10^8 PFU/mL administered 3 weeks after the first dose, then every 2 weeks. Total volume of Imlygic was up to 4.0 mL per treatment session. It may not be possible to inject all lesions at each treatment visit or over the full course of treatment. Previously injected and/or uninjected lesions may be injected at subsequent treatment visits. Continue treatment for at least 6 months unless other treatment is required or until there are no injectable lesions to treat. Imlygic may be reinitiated if new unresectable cutaneous, subcutaneous, or nodal lesions appear after a complete response. Refer to the Appendix for injection volume associated with lesion size.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for melanoma (version 1.2020 – December 19, 2019) list Imlygic as an option in multiple treatment situations, including as primary and second-line treatment for Stage III melanoma; for recurrent disease (including nodal recurrence), and second-line or subsequent therapy; for disseminated metastatic disease; and in combination with Yervoy (ipilimumab injection), for metastatic or unresectable disease following disease progression or maximal clinical benefit from BRAF targeted therapy.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Imlygic. Because of the specialized skills required for evaluation and diagnosis of patients treated with Imlygic as well as the monitoring required for adverse events and long-term efficacy, approval requires Imlygic to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Imlygic is recommended in those who meet the following criteria:

FDA-Approved Indications

E) Melanoma. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy (This includes reinitiation in patients with new lesions following a complete response). Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

i. The patient is ≥ 18 years of age; AND

ii. Imlygic will be directly injected into advanced, metastatic, recurrent, or unresectable cutaneous, subcutaneous, or nodal lesions; AND

iii. Imlygic will be administered by or under the supervision of an oncologist, dermatologist, or surgeon.

B) Patient is Currently Receiving Imlygic. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. The patient has remaining injectable lesions for treatment; AND

ii. According to the prescriber, the patient has not experienced clinically relevant disease progression (e.g., disease progression associated with a decline in performance status and/or alternative therapy was needed); AND

iii. Imlygic will be administered by or under the supervision of an oncologist, dermatologist, or surgeon.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Imlygic has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Concurrent Use with Anti-Herpetic Viral Agents.** Imlygic is a genetically modified, live, attenuated HSV-1 that is sensitive to acyclovir. Anti-herpetic viral agents (e.g., acyclovir, valacyclovir, famciclovir) may interfere with efficacy.

2. **Immoncompromised Patients.** Imlygic is contraindicated in patients who are immunocompromised, including those with a history of primary or acquired immunodeficient states, leukemia, lymphoma, acquired immunodeficiency syndrome (AIDS), or other clinical manifestations of infection with human immunodeficiency viruses, and those on immunosuppressive therapy.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Imlygic intralesional injection [prescribing information]. Thousand Oaks, CA: BioVex/Amgen; December 2018.
2. Dharmadhikari N, Mehnert JM, Kaufman HL. Oncolytic virus immunotherapy for melanoma. *Curr Treat Options Oncol*. 2015;16(3):326.
3. Moehler M, Goepfert K, Heinrich B, et al. Oncolytic virotherapy as emerging immunotherapeutic modality: potential of parvovirus h-1. *Front Oncol*. 2014;4:92.
4. The NCCN Melanoma Clinical Practice Guidelines in Oncology (Version 1.2020 – December 19, 2019). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 13, 2020.

HISTORY

Type of Revisior	Summary of Changes	Date Reviewed
New Policy	--	02/20/2019
Annual revision	**Melanoma:** Clarify that criteria apply to patients with advanced disease.	02/19/2020

APPENDIX

Lesion Size (longest dimension)	Injection volume
> 5 cm	Up to 4 mL
> 2.5 cm to 5 cm	Up to 2 mL
> 1.5 cm to 2.5 cm	Up to 1 mL
> 0.5 cm to 1.5 cm	Up to 0.5 mL
≤ 0.5 cm	Up to 0.1 mL

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Ixempra Prior Authorization Policy

- Ixempra® (ixabepilone injection for intravenous use – R-Pharm US)

REVIEW DATE: 12/16/2020

OVERVIEW

Ixempra, a microtubule inhibitor, is indicated in combination with capecitabine for the treatment of patients with metastatic or locally advanced **breast cancer** resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated.[1] Ixempra is indicated as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine.

Anthracycline resistance is defined as progression while on therapy or within 6 months in the adjuvant setting or 3 months in the metastatic setting.[1] Taxane resistance is defined as progression while on therapy or within 12 months in the adjuvant setting or 4 months in the metastatic setting.

Guidelines

The National Comprehensive Cancer Network (NCCN) **breast cancer** (version 6.2020 – September 8, 2020) clinical practice guidelines recommend Ixempra as a single agent for recurrent or stage IV human epidermal growth factor receptor 2 (HER2)-negative disease and in combination with trastuzumab for HER2-positve disease.[2,3]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Ixempra. All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Ixempra as well as the monitoring required for adverse events and long-term efficacy, approval requires Ixempra to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ixempra is recommended in those who meet the following criteria:

FDA-Approved Indications

182. Breast Cancer. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient has recurrent or metastatic disease; AND

B) Ixempra is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ixempra is not recommended in the following situations:

183. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

590. Ixempra® injection for intravenous use [prescribing information]. Princeton, NJ: R-Pharm US; January 2016.
591. The NCCN Drugs & Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 9, 2020. Search term: ixabepilone.
592. The NCCN Breast Cancer Clinical Practice Guidelines (Version 6.2020 – September 8, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 9, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/18/2019
Annual Revision	No criteria changes.	12/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Jevtana® (cabazitaxel injection for intravenous use – Sanofi-Aventis LLC)

DATE REVIEWED: 02/26/2020

OVERVIEW

Jevtana is a microtubule inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) previously treated with a docetaxel-containing treatment regimen.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) prostate cancer guidelines (version 4.2019 – August 19, 2019) lists Jevtana as one of the category 1 recommended therapies in the post-docetaxel setting for metastatic CRPC.[2,3] The guidelines note that Jevtana (in combination with steroid) can be considered in patients who are not candidates for docetaxel or are intolerant to docetaxel; however, current data do not support greater efficacy of Jevtana over docetaxel.[2]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Jevtana. Because of the specialized skills required for evaluation and diagnosis of patients treated with Jevtana as well as the monitoring required for adverse events and long-term efficacy, approval requires the medication to be prescribed by or in consultation with a prescriber who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Jevtana is recommended in those who meet the following criteria:

FDA-Approved Indications

4. Prostate Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** The patient has metastatic castration-resistant prostate cancer; AND
- **B)** The medication will be used in combination with a systemic corticosteroid (e.g., prednisone); AND
- **C)** The patient meets one of the following criteria (i or ii):
  - **i.** The patient has been previously treated with a docetaxel-containing treatment regimen; OR
  - **ii.** The patient is not a candidate or is intolerant to docetaxel therapy, according to the prescriber; AND
- **D)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Jevtana has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

274. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

432. Jevtana™ Intravenous Infusion [prescribing information]. Bridgewater, NJ: Sanofi-Aventis; January 2018.
433. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 20, 2020. Search term: cabazitaxel.
434. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (Version 4.2019 – August 19, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 21, 2020.

HISTORY

Type of Revision	Summary of Changes*	Date Reviewed
New Policy	New criteria	09/11/2019
Early annual revision	No criteria changes	02/26/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Kadcyla Prior Authorization Policy
- Kadcyla® (ado-trastuzumab emtansine for intravenous [IV] injection – Genentech)

REVIEW DATE: 08/12/2020

OVERVIEW

Kadcyla is indicated for the treatment of patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer in the following settings:[1]
- **Early breast cancer**, as a single agent, for the adjuvant treatment in patients who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.

- **Metastatic breast cancer**, in patients who previously received trastuzumab and a taxane, separately or in combination. Patients should have either received prior therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy.

Guidelines

- **Breast cancer:** The National Comprehensive Cancer Network (NCCN) breast cancer guidelines (version 5.2020 – July 15, 2020) recommend Kadcyla as a preferred adjuvant therapy in patients who have residual disease after receiving neoadjuvant (preoperative) therapy (category 1).[2,3] Kadcyla is also recommended for the treatment of HER2-positive recurrent or Stage IV metastatic disease (category 2A).
- **Non-small cell lung cancer:** The NCCN non-small cell lung cancer (NSCLC) guidelines (version 6.2020 – June 15, 2020) and Compendium recommend Kadcyla for HER2 mutation-positive NSCLC (category 2A).[3,4]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Kadcyla. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Kadcyla, as well as the monitoring required for adverse events and long-term efficacy, approval requires Kadcyla to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kadcyla is recommended in those who meet the following criteria:

FDA-Approved Indications

26. Breast Cancer. Approve if the patient meets the following criteria (A, B, and C):
- **A)** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
- **B)** Patient meets ONE of the following criteria (i or ii):
  - **i.** Approve for 1 year if Kadcyla is used for recurrent or metastatic breast cancer; OR
  - **ii.** Approve for 1 year (total) if Kadcyla will be used as adjuvant therapy; AND
- **C)** Kadcyla is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

2. Non-Small Cell Lung Cancer (NSCLC). Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient has human epidermal growth factor receptor 2 (HER2) mutation-positive non-small cell lung cancer; AND
- **B)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kadcyla is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

435. Kadcyla® for intravenous injection [prescribing information]. South San Francisco, CA: Genentech, Inc.; May 2019.
436. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 5.2020 – July 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed August 10, 2020.
437. The NCCN Drugs & Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 10, 2020. Search term: ado-trastuzumab emtansine.
438. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 6.2020 – June 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 10, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	No changes to criteria.	06/27/2018
Annual revision	Changed Breast Cancer criteria to a regular PA from pharmacogenomic PA. Added criteria for treatment of metastatic disease and for adjuvant therapy. Also added requirement for prescriber specialty. Added new approval condition for non-small cell lung cancer with HER2 mutation based on NCCN guidelines/Compendium support.	07/24/2019
Annual revision	No criteria changes	08/12/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Keytruda Prior Authorization Policy

- Keytruda® (pembrolizumab for injection, for intravenous use and injection for intravenous use – Merck & Co., Inc.)

REVIEW DATE: 06/17/2020; selected revision 12/02/2020

OVERVIEW

Keytruda, a human programmed death receptor-1 (PD-1) blocking antibody, is indicated for the treatment of the following indications:[1]

- **Breast cancer, triple-negative**, in combination with chemotherapy for the treatment of patients with locally recurrent unresectable or metastatic disease whose tumors express PD-L1 (combined positive score [CPS] ≥ 10) as determined by an FDA-approved test.*
- **Cervical cancer**, for treatment of patients with recurrent or metastatic disease with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.*
- **Classical Hodgkin lymphoma**, in the following situations:
  - For treatment of adult patients with relapsed or refractory disease.
  - For the treatment of pediatric patients with refractory disease, or disease that has relapsed after two or more prior lines of therapy.
- **Cutaneous squamous cell carcinoma,** treatment of patients with recurrent or metastatic disease that is not curable by surgery or radiation.
- **Endometrial cancer**, in combination with Lenvima (lenvatinib capsules), for the treatment of patients with advanced disease that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.
- **Esophageal cancer**, treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 (CPS ≥ 10) as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.

- **Gastric cancer**, for treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test, with disease progression on or after two or more lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, human epidermal growth factor receptor 2 (HER2)/neu-targeted therapy.*
- **Head and neck squamous cell carcinoma**, in the following situations:
  - As a single agent for the treatment of recurrent or metastatic disease with disease progression on or after platinum-containing chemotherapy; AND
  - In combination with platinum and fluorouracil (FU) for the first-line treatment of patients with metastatic or with unresectable, recurrent disease; AND
  - As a single agent, for the first line treatment of patients with metastatic or with unresectable, recurrent disease whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.
- **Hepatocellular carcinoma**, for treatment of patients who have been previously treated with Nexavar® (sorafenib tablets).*
- **Melanoma**, for the treatment of patients with unresectable or metastatic disease. Keytruda is also indicated for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.
- **Merkel cell carcinoma**, for adult and pediatric patients with recurrent, locally advanced, or metastatic disease.*
- **Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)**, for treatment of adult and pediatric patients with unresectable or metastatic disease, in the following situations:
  - solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options;* OR
  - colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.*

  Limitation of Use: The safety and effectiveness of Keytruda in pediatric patients with MSI-H central nervous system cancers have not been established.
- **Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer,** for the first-line treatment of patients with unresectable or metastatic disease.
- **Non-small cell lung cancer** (**NSCLC**), in the following situations:
  - As a single agent for the first-line treatment of patients whose tumors have high PD-L1 expression (tumor proportion score [TPS] ≥ 1%) as determined by an FDA-approved test, with no epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations, and is stage III where patients are not candidates for surgical resection or definitive chemoradiation or for metastatic disease; AND
  - As a single agent for the treatment of patients with metastatic disease whose tumors express PD-L1 (TPS ≥ 1%) as determined by an FDA-approved test and with disease progression on or after platinum-containing chemotherapy. Patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Keytruda; AND
  - In combination with Alimta® (pemetrexed intravenous injection) and platinum-based chemotherapy, for the first-line treatment of patients with metastatic nonsquamous NSCLC with no *EGFR* or *ALK* genomic tumor aberrations; AND
  - In combination with carboplatin and either paclitaxel or Abraxane® (nab-paclitaxel injection), for first-line treatment in metastatic squamous NSCLC.
- **Primary mediastinal large B-cell lymphoma** (PMBCL), for treatment of adult and pediatric patients with refractory disease, or who have relapsed after two or more prior lines of therapy.
  Limitation of Use: Keytruda is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

- **Renal cell carcinoma**, in combination with Inlyta (axitinib tablets), for the first-line treatment of patients with advanced disease.
- **Small cell lung cancer**, for treatment of metastatic disease and disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.*
- **Tumor mutational burden-high (TMB-H) cancer**, treatment of adult and pediatric patients with unresectable or metastatic disease (≥ 10 mutations/megabase), as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.*
  Limitation of Use: The safety and effectiveness of Keytruda in pediatric patients with TMB-H central nervous system (CNS) cancers have not been established.
- **Urothelial carcinoma**, in the following situations:
  - Treatment of locally advanced or metastatic disease in patients who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (CPS ≥ 10) as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status;* AND
  - Treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; AND
  - Treatment of Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer with carcinoma in situ with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

*This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Keytruda. Because of the specialized skills required for evaluation and diagnosis of patients treated with Keytruda as well as the monitoring required for adverse events and long-term efficacy, approval requires the medication to be prescribed by or in consultation with a prescriber who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Keytruda is recommended in those who meet one of the following criteria:

FDA-Approved Indications

2. Breast Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
- **A)** Patient has locally unresectable or metastatic disease; AND
- **B)** Patient has triple-negative breast cancer (i.e., estrogen receptor-negative, progesterone receptor-negative, human epidermal growth factor receptor 2 [HER2]-negative); AND
- **C)** The medication is used in combination with chemotherapy; AND
- **D)** Patient's tumor expression for programmed death-ligand 1 (PD-L1) as determined by an approved test has a combined positive score (CPS) ≥ 10; AND
- **E)** The medication is prescribed by or in consultation with an oncologist.

Note: Also see **Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors**.

3. **Cervical Cancer.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   A) Patient has tried chemotherapy; AND
   Note: Examples of chemotherapy are cisplatin, paclitaxel, bevacizumab, topotecan, carboplatin).
   B) Patient's tumor expression for programmed death-ligand 1 (PD-L1), as determined by an approved test, has a combined positive score (CPS) ≥ 1; AND
   C) The medication is prescribed by or in consultation with an oncologist.

   Note: Also see **Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors.**
4. **Classic Hodgkin Lymphoma.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient meets ONE of the following (i or ii):
      i. Patient meets both of the following criteria (a and b):
         a) Patient is ≥ 18 years of age; AND
         b) Patient has tried at least one systemic regimen.
         Note: Examples of systemic regimens are ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone + rituximab), Adcetris (brentuximab vedotin for injection), DHAP (dexamethasone, cisplatin, high-dose cytarabine), bendamustine.
      ii. Patient meets BOTH of the following criteria (a and b):
         a) Patient is < 18 years of age; AND
         b) Patient has tried at least two systemic regimens; AND
         Note: Examples of systemic regimens include AVPC (doxorubicin, vincristine, prednisone, cyclophosphamide), ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide), OEPA (vincristine, etoposide, prednisone, doxorubicin), Adcetris (brentuximab vendotin) with one of bendamustine, gemcitabine, or Opdivo (nivolumab for injection), DHAP (dexamethasone, cytarabine, cisplatin).
   B) The medication is prescribed by or in consultation with an oncologist.

5. **Cutaneous Squamous Cell Carcinoma.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   A) Patient has recurrent or metastatic disease; AND
   B) The disease is not curable by surgery or radiation; AND
   C) The medication is prescribed by or in consultation with an oncologist.

6. **Endometrial Carcinoma.** Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
   A) Disease is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND
   B) The medication is used in combination with Lenvima™ (lenvatinib capsules); AND
   C) Patient has progressed on at least one prior systemic therapy; AND
   Note: Examples of systemic therapy are carboplatin, paclitaxel, docetaxel, cisplatin, doxorubicin, ifosfamide, everolimus, letrozole.
   D) Patient is not a candidate for curative surgery or radiation; AND
   E) The medication is prescribed by or in consultation with an oncologist.

   Note: Also see **Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors.**

6. **Esophageal and Esophagogastric Junction Cancer.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient meets one of the following criteria (i or ii):

i. Patient meets BOTH of the following criteria (a and b):
  a) Patient's tumor expression for programmed death-ligand 1 (PD-L1) as determined by an approved test has a combined positive score (CPS) ≥ 10; AND
  b) Patient has tried at least one previous chemotherapy regimen; OR
  Note: Examples of chemotherapy regimens are fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin, fluoropyrimidine and cisplatin, paclitaxel with cisplatin or carboplatin, docetaxel with cisplatin.

ii. Patient meets BOTH of the following criteria (a and b):
  a) Patient's tumor expression for programmed death-ligand 1 (PD-L1) as determined by an approved test has a combined positive score (CPS) ≥ 1; AND
  b) Patient has tried at least two previous chemotherapy regimens; AND
  Note: Examples of chemotherapy regimens are fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin, fluoropyrimidine and cisplatin, paclitaxel with cisplatin or carboplatin, docetaxel with cisplatin.

B) The medication is prescribed by or in consultation with an oncologist.

Note: Also see **Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors.**

7. **Gastric Cancer.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   C) Patient's tumor expression for programmed death-ligand 1 (PD-L1) as determined by an approved test has a combined positive score (CPS) ≥ 1; AND
   D) Patient has tried at least two previous chemotherapy regimens; AND
   Note: Examples of chemotherapy regimens are fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin, fluoropyrimidine and cisplatin, paclitaxel with cisplatin or carboplatin, docetaxel with cisplatin 5.
   E) If the patient's tumor is human epidermal growth factor receptor 2 (HER2) or HER2/neu positive, targeted therapy with trastuzumab has been tried; AND
   F) The medication is prescribed by or in consultation with an oncologist.

   Note: Also see **Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors.**

8. **Head and Neck Squamous Cell Carcinoma (HNSCC).** Approve for 1 year if the patients meets the following (A, B, and C):
   A) Patient has recurrent or metastatic disease; AND
   B) Patient meets one of the following criteria (i or ii):
     i. If the medication is used for first-line treatment, patient has to meet one of the following criteria (a or b):
       a) Keytruda is used in combination with chemotherapy; OR
       Note: Examples of chemotherapy are cisplatin, carboplatin, fluorouracil.
       b) Keytruda is used as a single agent if the tumors are PD-L1-positive (combined positive score ≥ 1), as determined by an approved test.
     ii. For subsequent therapy, patient has tried at least one platinum-containing chemotherapy regimen; AND
     Note: Examples of platinum-contain chemotherapy regimens are: cisplatin or carboplatin with Erbitux® [cetuximab intravenous infusion], gemcitabine, or 5-fluorouracil [5-FU].
   C) The medication is prescribed by or in consultation with an oncologist.

9. **Hepatocellular Carcinoma, Including Hepatobiliary Cancers**. Approve for 1 year if the patient meets the following conditions (A and B):
   A) Patient has tried at least one tyrosine kinase inhibitor; AND

Note: Examples of tyrosine kinase inhibitors include Nexavar (sorafenib tablets) and Lenvima (levatinib capsules).

B) The medication is prescribed by or in consultation with an oncologist.

Note: Also see **Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors.**

10. Melanoma [Note: This includes cutaneous melanoma, brain metastases due to melanoma and uveal melanoma]. Approve for the duration noted below if the patient meets BOTH of the following (A and B):

A) Patient meets ONE of the following (i or ii):

i. Approve for 1 year if the patient has unresectable, advanced, or metastatic melanoma; OR

ii. Approve for up to 1 year (total) if Keytruda will be used as adjuvant treatment; AND
Note: For example, in a patient with no evidence of disease following resection of node-positive disease, locoregional recurrence, or in transit recurrence.

B) The medication is prescribed by or in consultation with an oncologist.

11. Merkel Cell Carcinoma. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient has recurrent, locally advanced, or metastatic disease; AND

B) The medication is prescribed by or in consultation with an oncologist.

12. Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors. Note**:** Examples of solid tumors with MSI-H or dMMR are breast cancer, biliary tract cancers, gastric, gastroesophageal or esophageal cancers, colon or rectal cancer, Ewing sarcoma, occult primary (cancer of unknown primary), osteosarcoma, mesenchymal chondrosarcoma, poorly differentiated neuroendocrine tumor, pancreatic adenocarcinoma, endometrial carcinoma, penile, adrenal gland, vulvar, cervical, ovarian, fallopian tube, primary peritoneal, small bowel adenocarcinoma, testicular cancer. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) One of the following conditions apply (i, ii, or iii):

i. Patient has tried at least one prior systemic therapy for an MSI-H or dMMR solid tumor); OR

ii. Patient has unresectable or metastatic gallbladder cancer (including intra- and extra-hepatic cholangiocarcinoma); OR

iii. Patient has unresectable or metastatic colon or rectal cancer.

B) The medication is prescribed by or in consultation with an oncologist.

13. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, and C):

A) Patient has advanced or metastatic disease; AND

B) Patient meets one of the following (i, ii, or iii):

i. The tumor proportion score (TPS) for PD-L1 as determined by an approved test is ≥ 1% AND the tumor is negative for targetable mutations; OR
Note: In this setting, Keytruda can be used in both non-squamous (that is, adenocarcinoma, large cell, or NSCLC not otherwise specified) and squamous cell carcinoma, either as first-line or continuation maintenance therapy.

ii. Patient has non-squamous cell carcinoma (that is, adenocarcinoma, large cell, or NSCLC not otherwise specified) and meets one of the following (a or b):

a) The tumor is negative for actionable mutations and the medication is used first-line in combination with platinum chemotherapy (that is, carboplatin or cisplatin) and Alimta (pemetrexed for injection); OR

b) Patient has previously received targeted drug therapy for actionable mutation; OR
Note: Examples of actionable mutations include sensitizing epidermal growth factor receptor [*EGFR*] mutation, anaplastic lymphoma kinase [*ALK*] fusions, *RET* rearrangement positive, *MET* exon 14 skipping, *NTRK* gene fusion positive, *BRAF V600E* mutation positive, and *ROS1* rearrangement positive.

iii. Patient has squamous cell carcinoma and meets one of the following (a or b):

Note: Keytruda can be used in this setting regardless of the PD-L1 expression levels.

a) The tumor is negative for actionable mutations and the medication is used first-line in combination with platinum chemotherapy (that is, carboplatin or cisplatin) and either one of paclitaxel or Abraxane (paclitaxel protein-bound for injection); OR

b) Patient has previously received targeted drug therapy for an actionable mutation; AND
Note: Examples of actionable mutations include sensitizing epidermal growth factor receptor [*EGFR*] mutation, anaplastic lymphoma kinase [*ALK*] fusions, *RET* rearrangement positive, *MET* exon 14 skipping, *NTRK* gene fusion positive, *BRAF V600E* mutation positive, and *ROS1* rearrangement positive.

C) The medication is prescribed by or in consultation with an oncologist.

14. Primary Mediastinal Large B-Cell Lymphoma. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient has relapsed after, or is refractory to, at least two previous regimens; AND
Note: Examples of previous regimens include autologous hematopoietic stem cell transplant (auto-HSCT), EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab), RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone], RCEPP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone).

B) The medication is prescribed by or in consultation with an oncologist.

15. Renal Cell Carcinoma. Approve for 1 year if the patient meets BOTH of the following (A, B, and C):

A) Patient has advanced disease; AND

B) The medication is used in combination with Inlyta (axitinib tablets); AND

C) The medication is prescribed by or in consultation with an oncologist.

16. Small Cell Lung Cancer. Approve for 1 year if the patient meets BOTH of the following criteria (A and B):

A) Patient has tried at least one other chemotherapy regimen; AND
Note: Examples of chemotherapy regimen are cisplatin, carboplatin, etoposide, irinotecan, topotecan, paclitaxel.

B) The medication is prescribed by or in consultation with an oncologist.

17. Tumor Mutational Burden-High (TMB-H) Cancer. Approve for 1 year if the patient meets the following (A, B, and C):

A) Patient has unresectable or metastatic tumor mutational burden-high (≥ 10 mutations/megabase) solid tumor; AND
Note: Examples of solid tumors are anal cancer, cervical cancer, chondrosarcoma, chordoma, endometrial carcinoma, Ewing sarcoma, mesothelioma cancer, neuroendocrine cancer, osteosarcoma, salivary gland tumors, small cell lung cancer, thyroid cancer, uterine sarcoma, vulvar cancer.

B) Patient has progressed on prior therapy; AND

C) Patient has no satisfactory alternative treatment options.

18. Urothelial Carcinoma. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient meets ONE of the following conditions (i, ii, iii, or iv):

i. Patient has tried at least one platinum-based chemotherapy; OR
Note: Cisplatin and carboplatin are platinum-based chemotherapies.

ii. Patient meets both of the following (a and b):

a) According to the prescriber, patient is not eligible for cisplatin-based chemotherapy, AND

b) The tumor expresses PD-L1, defined as a combined positive score (CPS) ≥ 10; OR

iii. According to the prescriber, patient is not eligible for platinum-based chemotherapy (i.e., with cisplatin and carboplatin); OR
Note: This is regardless of PD-L1 status.

iv. Patient meets both of the following (a and b):

a) Patient has non-muscle invasive bladder cancer; AND

b) Patient has tried Bacillus Calmette-Guerin (BCG) or intravesical chemotherapy; AND
Note: Examples of agents used as intravesical chemotherapy include mitomycin and gemcitabine.

B) The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

19. Anal Carcinoma. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient has received at least one other chemotherapy regimen; AND
Note: Examples of chemotherapy regimens are 5-fluorouracil (5-FU), cisplatin, carboplatin, paclitaxel, FOLFOX (oxaliplatin, leucovorin, and 5-FU).

B) The medication is prescribed by or in consultation with an oncologist.

20. Gestational Trophoblastic Neoplasia. Approve for 1 year if the patient meets the following criteria (A and B):

A) The patient meets one of the following (i or ii):

i. Patient has tried at least one previous chemotherapy regimen for recurrent or progressive disease; OR
Note: Examples of chemotherapy regimens contain etoposide, cisplatin/carboplatin, paclitaxel, bleomycin, ifosfamide, methotrexate.

ii. Patient has methotrexate-resistant high-risk disease; AND

B) The medication is prescribed by or in consultation with an oncologist.

21. Malignant Pleural Mesothelioma. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient has tried first-line chemotherapy; AND
Note: Examples of chemotherapy are Alimta (pemetrexed intravenous injection) with or without cisplatin or carboplatin, gemcitabine plus cisplatin, vinorelbine.

B) The medication is prescribed by or in consultation with an oncologist.

22. Mycosis Fungoides/Sezary Syndrome. Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

23. Extranodal NK/T-Cell Lymphoma, Nasal Type. Approve for 1 year if the patient meets the following criteria (A and B):

A) The patient has received an asparaginase-based chemotherapy regimen; AND
Note: Examples of asparaginase-based chemotherapy are dexamethasone, ifosfamide, pegaspargase, etoposide; and gemcitabine, pegaspargase, oxaliplatin.

B) The medication is prescribed by or in consultation with an oncologist.

24. Thymic Carcinoma. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient has tried at least one other chemotherapy regimen; AND
Note: Examples of chemotherapy regimen are carboplatin, paclitaxel, cisplatin, doxorubicin, cyclophosphamide.

B) The medication is prescribed by or in consultation with an oncologist.

25. Vulvar Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):

A) The tumors are PD-L1-positive (combined positive score ≥ 1), as determined by an approved test; AND

B) Patient has tried at least one other chemotherapy regimen.
Note: Examples of chemotherapy regimen are cisplatin, carboplatin, fluorouracil, paclitaxel; AND

C) The medication is prescribed by or in consultation with an oncologist.

Note: Also see **Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors** and **Tumor Mutational Burden-High (TMB-H) Cancer.**

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Keytruda is not recommended in the following situations:

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	• **Cervical Cancer:** New FDA approved indication was added. • **cHL:** Criteria were revised to include patients of all ages who have one of the following: the patient has had an auto-HSCT and post-transplant Adcetris therapy, the patient has had ≥ 3 lines of systemic therapy and this includes an auto-HSCT as one line of therapy, or the patient is ineligible for transplant. Previously, criteria were separated by age groups. • **MSI-H or dMMR CRC:** Removed criterion that CRC is MSI-H or dMMR since this is in the indication. • **NSCLC:** For the criterion of Keytruda will be used in combination with Alimta and carboplatin, cisplatin was added as an alternative to carboplatin. • **PMBCL:** New FDA approved indication was added. • **Anal Carcinoma:** New indication recommended by NCCN guidelines was added. • **Brain Metastases Due to Melanoma or NSCLC:** Criteria were revised to add patients newly diagnosed with asymptomatic metastases. • **Melanoma, Uveal:** New indication was added based on NCCN guidelines. • **Extended Approval:** Throughout the policy revised to add "or stable disease". • **Duration of Therapy:** Throughout the policy revised so the patient has a response or stable disease as determined by the prescribing physician. • **Other Cancer-Related Indications:** Nasopharyngeal HNSCC (category 2B) was added. Cervical cancer and vulvar cancer were removed and added to the MSI-H or dMMR CRC discussion.	06/20/2018
Update 06/21/18	• The indication for urothelial carcinoma in the overview was updated based on revised prescribing information. The wording of the indication for treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy was revised to add "and whose tumors express PD-L1 (CPS ≥ 10), or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status."	Not applicable
Annual revision	**All Indications** • Changed approval duration to 1 year (previously was 6 months). • Removed response criteria for continuation of therapy (now must meet PA criteria for reauthorization). • Removed requirement in dosing section that Keytruda is infused over 30 minutes. **Brain Metastases Due to Melanoma or NSCLC, Uveal Melanoma, Patient has been Started on Keytruda** • Conditions were deleted and are now generally included under respective cancers (melanoma and NSCLC). For patients already started on Keytruda, patients must meet criteria and dosing for continuation of therapy. **Cervical Cancer** • Since chemotherapy is required, delete requirement that the patient has recurrent or metastatic disease (presumed to be recurrent or metastatic if chemotherapy has been tried). • Simplify list of therapies that may have been tried so as to clarify that specific regimens are not required to be tried prior to Keytruda but are examples that may be tried as part of a regimen for cervical cancer. • Remove criterion that requires Keytruda be administered as a single agent (not needed). **Classic Hodgkin Lymphoma** • Since multiple therapies or stem cell transplant is required, delete requirement that the patient has relapsed or progressive disease (presumed to be relapsed or recurrent if multiple therapies has been tried). • Remove criterion that requires Keytruda be administered as a single agent (not needed). • For an exception to the requirement that the patient is required to have tried 3 previous lines of therapy, remove requirement that patients undergoing stem cell transplantation must undergo an autologous procedure (allogeneic procedures also mentioned in guidelines). To align with guidelines, remove requirement that the patient received post-transplant therapy with Adcetris. **Gastric, Gastroesophageal Junction, or Esophageal Cancer** • Since chemotherapy is required, delete requirement that the patient has locally advanced or metastatic disease (presumed to be locally advanced or metastatic if chemotherapy has been tried).	12/19/2018

	• Remove criterion that requires Keytruda be administered as a single agent (not needed). **Head and Neck Squamous Cell Carcinoma (HNSCC)** • Since chemotherapy is required unless contraindicated, delete requirement that the patient has recurrent or metastatic disease (presumed to be recurrent or metastatic if chemotherapy has been tried). Since used in nasopharyngeal disease, remove requirement that the patient has non-nasopharyngeal HNSCC. • Remove criterion that required the patient has disease progression on or after trying platinum-containing chemotherapy. For the criterion that requires a previous trial of chemotherapy, add cisplatin and carboplatin to the list of examples. • Remove criterion that requires Keytruda be administered as a single agent (not needed). **Hepatocellular Carcinoma, Including Hepatobiliary Cancers** • Add criteria to approve for this FDA-approved indication if the patient has tried at least one tyrosine kinase inhibitor, and if prescribed by or in consultation with an oncologist. **Melanoma** • Add a note to clarify that the criteria apply to cutaneous melanoma, brain metastasis due to melanoma, and uveal melanoma. • Add a criterion to approve for use of Keytruda in the adjuvant setting. **Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors** • When chemotherapy is required, delete requirement that the patient has unresectable or metastatic disease (presumed to be unresectable or metastatic if chemotherapy has been tried). • Remove criterion that requires Keytruda be administered as a single agent (not needed). • Add criteria to approve in the first-line setting for unresectable or metastatic gallbladder cancer. • For colon or rectal cancer simplify criteria to require a previous trial of chemotherapy (previously required progression while on a fluoropyrimidine or adjuvant therapy with FOLFOX). Remove requirement that patients who progressed after treatment with a fluoropyrimidine have not previously been treated with Keytruda or Opdivo. • For other MSI-H or dMMR solid tumors, change wording to require a trial of at least one prior systemic therapy (previously required disease progression). Remove requirement that there are no satisfactory alternative treatment options (not in guidelines for majority of these tumors). • Remove criterion that does not cover Keytruda for children with central nervous system tumors. **Non-Small Cell Lung Cancer** • When chemotherapy is required, delete requirement that the patient has metastatic disease (presumed to be metastatic if chemotherapy has been tried). • For non-squamous cell carcinoma, change criteria so that patients with unknown status for targetable mutations are not required to undergo testing (aligns with guidelines). • For patients with a tumor proportion score of ≥ 1% and ≥ 50%, remove criterion that requires Keytruda be administered as a single agent (not needed). For those with a tumor proportion score of at least 1%, remove criterion that excluded coverage if Keytruda, Opdivo, or Tecentiq have been used in the past. • To approve in the first-line setting, generally require use in combination with chemotherapy (applies to squamous and non-squamous histologies). Previously, use in the first-line setting only applied to non-squamous histology and required a specific regimen to be taken with Keytruda. • In the dosing section, clarify that dosing of 10 mg/kg given every 2 weeks and 2 mg/kg given every 3 weeks are approvable in patients with brain metastases. **Urothelial Carcinoma** • When chemotherapy is required, delete requirement that the patient has locally advanced or metastatic disease (presumed to be unresectable or metastatic if chemotherapy has been tried). • Remove criterion that requires Keytruda be administered as a single agent (not needed). • For patients that are not eligible for cisplatin, add that the tumor must express PD-L1. • Add criteria to allow an exception for patients who, according to the prescriber, are not eligible for platinum-based chemotherapy. Note that this is regardless of PD-L1 status. • Reword criteria to require a previous trial of at least one platinum-containing chemotherapy. Criteria previously required disease progression during or after trying one of these therapies.	

	Anal Carcinoma • Since chemotherapy is required, delete requirement that the patient has metastatic disease (presumed to be metastatic if chemotherapy has been tried). • Remove criterion that requires Keytruda be administered as a single agent (not needed). **Malignant Pleural Mesothelioma** • Remove criterion that requires Keytruda be administered as a single agent (not needed). • In dosing, add criteria to approve 200 mg as an intravenous infusion given once every 3 weeks. **Merkel Cell Carcinoma** • Move this condition to the FDA-Approved Uses section of the policy. Previously was approvable as an Other Uses With Supportive Evidence. • Change criteria to approve for recurrent, locally advanced, or metastatic disease, which aligns with the approved labeling. Criteria previously approved for disseminated disease. • Add 200 mg as an intravenous infusion given once every 3 weeks as an approvable dose. **Small Cell Lung Cancer** • Add this off-label indication as an approval, if the patient has tried at least one other systemic therapy within the past 6 months, and if prescribed by or in consultation with an oncologist. The approvable dose is 200 mg as an intravenous infusion given once every 3 weeks. **Other Cancer-Related Indications** • Remove nasopharyngeal head and neck cancer (included in criteria). Add T-cell lymphoproliferative disorders, chronic lymphocytic leukemia/small lymphocytic lymphoma, and gestational trophoblastic neoplasia to the list of oncology indications that are reviewed on a case-by-case basis by the Medical Director.	
Selected revision	**Melanoma:** For adjuvant treatment, criteria were changed to allow up to 1 year (total) of treatment. This aligns with the treatment duration for this use in the published study and for this indication in the Opdivo CC policy. Previously, criteria did not limit total treatment duration.	01/30/2019
Annual revision	**All Indications.** For Dosing, added "not more frequently than" with regards to frequency. If "e.g" are listed in criteria they were re-formatted to a Note. For criteria "Keytruda is prescribed by…" was changed to "The medication is prescribed by.." Where applicable, prescribing physician was changed to prescriber. **Endometrial Carcinoma**. New approval indication was added. **Esophageal and Esophagogastric Junction Cancer**. Previously was listed together with Gastric Cancer. Now, this indication is separated out since the guidelines are also separate for these conditions. **Gastric Cancer.** Deleted "Gastroesophageal Junction (GEJ) Cancer, or Esophageal Cancer" from indication. Criteria regarding the patient has tried a fluoropyrimidine and platinum was changed to "at least two previous chemotherapy regimens". **Head and Neck Squamous Cell Carcinoma**. The following criteria were added: the patient has recurrent or metastatic disease; for first-line setting, Keytruda is used in combination with chemotherapy or for use as single agent, the tumor has to be PD-L1-positive; for subsequent therapy, the wording was changed to at least one platinum-containing chemotherapy regimen has been tried. The other criteria providing exception for chemotherapy contraindication was deleted. **Melanoma.** Deleted criteria Keytruda will not be used in combination with Yervoy. **Microsatellite Instability High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors**. Added a list of different solid tumors in a Note under the indication as examples. Deleted the examples from within criteria. **Non-Small Cell Lung Cancer**. Modified criteria with regards to tumor proportion score for PD-L1 to state ≥ 1 and < 50% and added criteria that Keytruda is used as a single agent for maintenance. For non-squamous cell carcinoma with regards to targeted mutations, deleted criteria,"tumor is negative or unknown for these targetable mutations." **Renal Cell Carcinoma**. Added new approval condition and criteria. **Small Cell Lung Cancer.** Instead of systemic therapy, changed to "chemotherapy regimen". Deleted criteria "within the past 6 months" with regards to trying chemotherapy. **Anal Carcinoma**. Added "at least one" with regards to trying chemotherapy "regimen". **Gestational Trophoblastic Neoplasia.** Added new approval condition and criteria. **Mycosis Fungoides/Sezary Syndrome**. Added new approval condition and criteria.	12/11/2019

	Thymic Carcinoma. Added new approval condition and criteria. **Vulvar Cancer.** Added new approval condition and criteria. **Other Cancer-Related Indications**. Deleted to be in-line with other policies.	
Early annual revision	**Classic Hodgkin Lymphoma:** Examples of systemic therapies were moved to a Note (previously listed as examples within the criteria). **Endometrial Carcinoma:** Criteria were modified to allow coverage for a patient with recurrent disease, if other conditions are met. Previously, criteria only addressed advanced disease. **Hepatocellular Carcinoma, Including Hepatobiliary Cancers:** Examples of tyrosine kinase inhibitors were moved to a Note (previously listed as examples within the criteria). **Melanoma:** Examples of adjuvant therapy uses were moved to a Note (previously listed as examples within the criteria). **Non-Small Cell Lung Cancer:** Criteria that applied specifically to patients with a tumor proportion score (TPS) ≥ 1% and < 50% were deleted from the policy. Now all criteria for NSCLC apply to any patient with a TPS ≥ 1%. Criteria applying to a patient with non-squamous cell carcinoma were modified to be listed in a Note as examples of targetable mutations (previously listed as i.e. within the criteria). RET rearrangement positive, MET exon 14 skipping, NTRK gene fusion positive, BRAF V600E mutation positive, and ROS1 rearrangement positive were added to list of targetable mutations. **Urothelial Carcinoma:** Examples of platinum-based chemotherapies were moved to a Note (previously listed as examples within the criteria). Clarify in criteria that tumor expression of PD-L1 is defined by combined positive score (CPS) ≥ 10 (previously CPS was listed as an i.e. in the criteria). Criteria were added to approve Keytruda if the patient has non-muscle invasive bladder cancer and has tried Bacillus Calmette-Guerin (BCG) or intravesical chemotherapy. **Extranodal NK/T-Cell Lymphoma, Nasal Type:** To align with NCCN recommendations, this indication was added as an Other Use With Supportive Evidence. Criteria approve for 1 year if the patient has tried asparaginase-based chemotherapy regimen and if prescribed by or in consultation with an oncologist.	06/17/2020
Selected Revision	• **Breast Cancer:** Added new approval condition and criteria based on new FDA approval. • **Classic Hodgkin Lymphoma:** Aligned criteria with modified FDA-approved indication. Deleted references to transplant and modified examples to align with guidelines. Criteria separated for adult and pediatric patients based on the number of prior therapies required prior to Keytruda approval. • **Cutaneous Squamous Cell Cancer:** Added new approval condition and criteria based on FDA-approval. • **Hepatocellular Carcinoma, Including Hepatobiliary Cancers:** Added **Note** to see **Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors.** • **Microsatellite Instability High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors:** Added occult primary (cancer of unknown primary) and biliary tract cancers to list of examples. Endometrioid carcinoma changed to endometrial cancer. Modified colorectal cancer criteria to match FDA-approved use in first-line setting by deleting criteria for prior chemotherapy use and deleting criteria regarding patient not suitable for intensive therapy. Added "unresectable or metastatic" disease. • **Non-Small Cell Lung Cancer:** With regards to tumor proportion score (TPS) for PD-L1, added criteria that tumor is negative for targetable mutations. Included a Note under this criteria to clarify the conditions in which Keytruda can be used. Added new criteria for non-squamous and squamous cell carcinoma separately. Within these histologies, added criteria specifying use of Keytruda when the tumor is targetable mutation-positive or negative. • **Tumor Mutational Burden-High (TMB-H) Cancer:** Added new approval condition and criteria based on FDA-approved indication. • **Vulvar Cancer:** In the existing Note, added reference to see "Tumor Mutational Burden-High (TMB-H) Cancer."	12/02/2020

NSCLC – Non-small cell lung cancer; EGFR – Epidermal growth factor receptor; ALK – Anaplastic lymphoma kinase; cHL – Classic Hodgkin Lymphoma; HNSCC – Head and neck squamous cell carcinoma; MSI-H – Microsatellite Instability-High; dMMR – Mismatch Repair Deficient; PD-L1 – Programmed death-ligand 1; GEJ – Gastroesophageal Junction; NCCN – National Comprehensive Cancer Network; auto-HSCT – Autologous-hematopoietic stem cell transplantation; PMBCL – Primary Mediastinal Large B-Cell Lymphoma.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Kymriah® (tisagenlecleucel suspension for intravenous infusion – Novartis Oncology)

DATE REVIEWED: 04/29/2020

OVERVIEW

Kymriah, a CD19-directed genetically modified autologous T cell immunotherapy, is indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.[1] Kymriah is also indicated for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Regarding this specific indication, Kyrmiah is not indicated for treatment of patients with primary central nervous system lymphoma.[1] Kymriah has a Boxed Warning regarding cytokine release syndrome (CRS) and neurological toxicities. Due to these risks, Kymriah is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Kymriah REMS.[1]

Kymriah is supplied as a frozen suspension of genetically modified autologous T cells in infusion bag(s) labeled for the specific recipient.[1] Kymriah is shipped directly to the cell laboratory associated with the infusion center in a liquid nitrogen Dewar. The product and patient-specific labels are found inside the Dewar. Store the infusion bag in the vapor phase of liquid nitrogen (less than or equal to minus 120°C) in a temperature-monitored system. Kymriah should be thawed prior to infusion.

Clinical Efficacy

The efficacy of Kymriah in pediatric and young adults with relapsed or refractory B-cell precursor ALL was assessed in an open-label, multicenter, single-arm study called ELIANA.[1-2] Therapy consisted of lymphodepleting chemotherapy (fludarabine 30 mg/m^2 daily for 4 days and cyclophosphamide 500 mg/m^2 daily for 2 days) followed by a single Kymriah dose.[1-2] Among the 63 patients who were evaluable for efficacy in the Kymriah prescribing information, 83% of patients achieved complete remission or complete remission with incomplete blood count recovery.[1] The published study evaluated 75 patients and the overall remission rate (the rate of complete remission or complete remission with incomplete hematologic recovery) within 3 months was 81%.[2] The efficacy of Kymriah was assessed in an open-label, multicenter, single-arm trial called JULIET.[1,3] Patients were ≥ 18 years of age with relapsed or refractory DLBCL who had previously received at least two lines of chemotherapy (including Rituxan® [rituximab injection for intravenous use] and an anathracycline), or relapsed following autologous hematopoietic stem cell transplantation (HSCT).[1] A single Kymriah infusion was administered after 2 to 11 days following the completion of lymphodepleting chemotherapy which involved fludarabine and cyclophosphamide, or Treanda® (bendamustine injection for intravenous use). Lymphodepleting chemotherapy was not required if the patient's white blood cell count was < 1,000 cells/μL. In total, 160 patients were enrolled and 106 patients received Kymriah; 92 patients received product that was manufactured in the US. The efficacy evaluation population included 68 patients and the overall response rate was 50% (n = 34/68).

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for ALL (version 1.2020 – January 15, 2020) address Kymriah.[4,5] In Philadelphia chromosome-positive B-cell ALL, Kymriah is cited as a treatment option for patients < 26 years of age and with refractory disease or ≥ two relapses and failure of two tyrosine kinase inhibitors (TKIs) [category 2A]. For Philadelphia chromosome-negative B-cell ALL, Kymriah is listed as a therapy option for patients < 26 years of age and with refractory disease or ≥ two relapses (category 2A).

The NCCN guidelines for Pediatric ALL (version 2.2020 – November 25, 2019) recommends Kymriah for the treatment of patients with refractory or ≥ 2 relapses, TKI intolerant or refractory disease, or relapse post-hematopoietic stem cell transplantation (category 2A).[5,7] Kymriah is also recommended for patients who are minimal residual disease positive after consolidation therapy, and in Philadelphia chromosome-positive disease with less than complete response, or high-risk genetics.

The NCCN guidelines for B-cell lymphomas (version 1.2020 – January 22, 2020) recommend Kymriah for the treatment of the following relapsed or refractory disease after at least two course of systemic therapy: DLBCL following transformation from follicular lymphoma or nodal marginal zone lymphoma, DLBCL, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, AIDS-related B-cell lymphoma, human herpes virus 8 (HHV8)-positive DLBCL, and post-transplant lymphoproliferative disorders (category 2A).[5,6]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Kymriah. All approvals for initial therapy are provided for the initial approval duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Kymriah as well as the monitoring required for adverse events and long-term efficacy, approval requires Kymriah to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kymriah is recommended in those who meet the following criteria:

FDA-Approved Indications

183. Acute Lymphoblastic Leukemia, B-Cell Precursor. Approve a single dose if the patient meets the following criteria (A, B, C, D, and E):
- **C)** The patient is < 26 years of age; AND
- **D)** Kymriah is prescribed by or in consultation with an oncologist; AND
- **E)** The patient meets one of the following (i, ii, or iii):
  - a. The patient has disease that is refractory, or in second or later relapse; OR
  - b. The patient is minimal residual disease positive after consolidation therapy; OR
  - c. The patient is Philadelphia chromosome-positive and one of the following (a, b, c, or d):
    - i. Less than complete response; OR
    - ii. High-risk genetics; OR
    - iii. Tyrosine kinase inhibitor intolerant or refractory;
      Note: Tyrosine kinase inhibitors include Sprycel® (dasatinib tablets), imatinib tablets, Iclusig® (ponatinib tablets), Tasigna® (nilotinib capsules), and Bosulif® (bosutinib tablets); OR
    - iv. Relapse post-hematopoietic stem cell transplantation; AND
- **D)** The patient received lymphodepleting chemotherapy prior to Kymriah infusion: AND
- **E)** The patient has not been previously treated with Kymriah.

2. B-Cell Lymphoma. Approve a single dose if the patient meets the following criteria (A, B, C, D, E, and F):
- **A)** The patient meets one of the following diagnoses (i, ii, iii, iv, v, vi, vii, viii, or ix):
  - **i.** Large B-cell lymphoma; OR
  - **ii.** Diffuse large B-cell lymphoma; OR
  - **iii.** Primary mediastinal large B-cell lymphoma; OR

iv. High-grade B-cell lymphoma; OR
v. Diffuse large B-cell lymphoma arising from follicular lymphoma; OR
vi. Diffuse large B-cell lymphoma arising from nodal marginal zone lymphoma; OR
vii. Acquired immune deficiency syndrome (AIDS)-related B-cell lymphoma; OR
viii. Human Herpes Virus 8-positive diffuse large B-cell lymphoma; OR
ix. Post-transplant lymphoproliferative disorders, B-cell type; AND

B) The patient is ≥ 18 years of age; AND
C) Kymriah is prescribed by or in consultation with an oncologist; AND
D) Kymriah is being used for disease that is relapsed or refractory after two or more lines of systemic therapy; AND
E) The patient must meet one of the following (i or ii):
i. The patient received lymphodepleting chemotherapy prior to Kymriah infusion; OR
ii. The patient's white blood cell count is less than or equal to 1 x 10^9/L within 1 week prior to Kymriah infusion; AND
F) The patient has not been previously treated with Kymriah or Yescarta® (axicabtagene ciloleucel injection).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Kymriah has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

184. Re-treatment with Kymriah. Kymriah is for one time use, repeat dosing is not approvable.

185. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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598. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 1.2020 – January 22, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on April 17, 2020.
599. The NCCN Pediatric Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (Version 2.2020 – November 25, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on April 17, 2020.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/24/2019
Annual Revision	**Acute Lymphoblastic Leukemia:** Added additional criteria for approval including minimal residual disease positive after consolidation therapy; and for Philadelphia chromosome-positive disease – less than complete response, high-risk genetics, tyrosine kinase inhibitor intolerant or refractory disease, and relapse post-hematopoietic stem cell transplant.	04/29/2020

	B-cell lymphoma: Added approval criteria for diffuse large B-cell lymphoma arising from nodal marginal zone lymphoma. Revised criteria to not allow previous treatment with Yescarta.	

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Kyprolis Prior Authorization Policy
- Kyprolis (carfilzomib injection for intravenous use – Amgen/Onyx Pharmaceuticals)

REVIEW DATE: 03/10/2021

OVERVIEW

Kyprolis, a proteasome inhibitor, is approved for **multiple myeloma** the following situations:[1]
- for relapsed or refractory disease, in combination with dexamethasone ± Revlimid® (lenalidomide capsules) or Darzalex (daratumumab injection)/dexamethasone in patients who have received one to three lines of previous therapy.
- for relapsed or refractory disease, as a single agent in those who have received one or more lines of therapy.

Safety and efficacy is not established in patients < 18 years of age.

Guidelines

Kyprolis is discussed in guidelines from the National Comprehensive Cancer Network (NCCN).[2]
- **Multiple Myeloma:** The NCCN guidelines (version 4.2021 – December 10, 2020) recommend multiple therapeutic regimens that may be used for primary therapy and previously treated multiple myeloma.[3] For transplant and non-transplant candidates, Kyprolis/Revlimid/dexamethasone is recommended as an other regimen for primary treatment, and Kyprolis/cyclophosphamide/dexamethasone is among the regimens that are useful in certain circumstances. For previously treated multiple myeloma, multiple regimens are listed, including Kyprolis/Revlimid/dexamethasone and Kyprolis/Darzalex (daratumumab injection)/dexamethasone are among the Preferred regimens, whereas Kyprolis (twice weekly)/dexamethasone, Kyprolis/cyclophosphamide/dexamethasone, and Kyprolis/Pomalyst (pomalidomide capsules)/dexamethasone, are listed as other regimens. Kyprolis/Farydak (panobinostat capsules), Kyprolis/cyclophosphamide/Thalomid (thalidomide capsules)/dexamethasone, and Kyprolis (weekly)/dexamethasone are among the regimens that are useful in certain circumstances.
- **Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma:** In NCCN guidelines (version 1.2021 – September 1, 2020), Kyprolis/rituximab/dexamethasone is listed among other recommended regimens for primary treatment of Waldenstrom's Macroglobulinemia/lymphoplasmacytic lymphoma.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Kyprolis. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Kyprolis as well as the monitoring required for adverse events and long-term efficacy, approval requires Kyprolis to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kyprolis is recommended in those who meet one of the following criteria:

FDA-Approved Indications

14. Multiple Myeloma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
- **15.** Patient is ≥ 18 years of age; AND
- **16.** Patient meets ONE of the following (i or ii):
  - **A)** Kyprolis will be used in combination with Revlimid (lenalidomide capsules) and dexamethasone; OR
  - **B)** Patient has tried at least ONE prior regimen for multiple myeloma; AND
    Note: Examples include Velcade (bortezomib injection), Revlimid (lenalidomide capsules), Darzalex (daratumumab injection), Ninlaro (ixazomib capsules).
- **17.** The medication is prescribed by or in consultation with an oncologist or a hematologist.

Other Uses with Supportive Evidence

15. Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The medication will be used in combination with a rituximab product and dexamethasone; AND
- **C)** The medication is prescribed by or in consultation with an oncologist or a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kyprolis is not recommended in the following situations:

186. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Multiple Myeloma:** To align with other policies and NCCN guidelines, criterion for combination therapy was updated to require dexamethasone and Revlimid to be taken in combination with Kyprolis (previously required dexamethasone and at least one other agent with Revlimid listed as an example). In patients that had tried at least one other regimen, the criterion that required Kyprolis be used as part of a combination regimen was removed.	02/26/2020
Annual Revision	**Multiple Myeloma:** To be consistent with other oncology policies, the requirement that the patient is ≥ 18 years of age was added. **Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma:** To align with criteria for multiple myeloma, the requirement that the patient is ≥ 18 years of age was added.	03/10/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Levoleucovorin Products Prior Authorization Policy
- Fusilev® (levoleucovorin injection for intravenous use – Spectrum Pharmaceuticals)
- Khapzory™ (levoleucovorin injection for intravenous use – Spectrum Pharmaceuticals)
- Levoleucovorin injection for intravenous use – various manufacturers

REVIEW DATE: 06/17/2020

OVERVIEW

Levoleucovorin (Fusilev, Khapzory, generics) is the pharmacologically active, levo-isomer of racemic *d,l*-leucovorin.[1,2] Levoleucovorin is a chemically reduced derivative of folic acid, which can counteract the toxic and therapeutic effects of folic acid antagonists, such as methotrexate. In addition, levoleucovorin can enhance the therapeutic and toxic effects of fluoropyrimidines used in oncology.

Levoleucovorin is indicated:
- For rescue after high-dose methotrexate therapy in osteosarcoma, and
- To diminish the toxicity of impaired methotrexate elimination or overdosage of folic acid antagonists, and
- For use in combination chemotherapy with 5-fluorouracil in the treatment of patients with advanced metastatic colorectal cancer.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium recommends levoleucovorin use in combination with methotrexate for the treatment of gestational trophoblastic neoplasia, rhabdomyosarcoma, T-cell lymphomas, central nervous system cancers, B-cell lymphomas, chronic lymphocytic leukemia/small lymphocytic lymphoma, acute lymphoblastic leukemia, and osteosarcoma.[3] The NCCN Compendium recommends levoleucovorin use in combination with fluorouracil-based chemotherapy for the treatment of occult primary cancer, neuroendocrine and adrenal tumors, hepatocellular carcinoma, ovarian/fallopian tube/primary peritoneal cancer, thymomas and thymic carcinomas, esophageal and esophagogastric junction cancer, anal cancer, colon cancer, gastric cancer, small bowel adenocarcinoma, cervical cancer, rectal cancer, pancreatic adenocarcinoma, and bladder cancer.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of levoleucovorin. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because of the specialized skills required for evaluation and diagnosis of patients treated with levoleucovorin as well as the monitoring required for adverse events and long-term efficacy, approval requires levoleucovorin to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of levoleucovorin is recommended in those who meet the following criteria:

FDA-Approved Indications

184. Osteosarcoma. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Levoleucovorin is used in combination with high-dose methotrexate; AND
- **B)** Levoleucovorin is prescribed by or in consultation with an oncologist.

185. Colon or Rectal Carcinoma. Approve for 1 year if the patient meets the following criteria (A and B):

A) Levoleucovorin is used in combination with fluorouracil-based chemotherapy; AND

B) Levoleucovorin is prescribed by or in consultation with an oncologist.

186. Methotrexate Overdosage, or Impaired Methotrexate Elimination. Approve for 1 month.

Other Uses with Supportive Evidence

187. Cancer Diagnosis Currently Being Treated With Methotrexate. (Note: Examples include T-cell lymphoma, B-cell lymphoma, gestational trophoblastic neoplasm, central nervous system cancer). Approve for 1 year if levoleucovorin is prescribed by or in consultation with an oncologist.

188. Cancer Diagnosis Currently Being Treated With 5-Fluorouracil. (Note: Examples include hepatocellular carcinoma, ovarian cancer, gastric cancer, cervical cancer). Approve for 1 year if levoleucovorin is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Levoleucovorin has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

187. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

600. Fusilev® injection for intravenous use [prescribing information]. Irvine, CA: Spectrum Pharmaceuticals; January 2020.
601. Khapzory™ injection for intravenous use [prescribing information]. Irvine, CA: Spectrum Pharmaceuticals; March 2020.
602. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 8, 2020. Search term: levoleucovorin.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	06/18/2019
Annual Revision	**Methotrexate Overdosage, Inadvertent, or Impaired Methotrexate Elimination**: Removed "Inadvertent" from indication.	06/17/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Libtayo Prior Authorization Policy

- Libtayo® (cemiplimab-rwlc injection, for intravenous use – Regeneron/Sanofi Genzyme)

REVIEW DATE: 10/28/2020; 03/03/2021 selected revision

OVERVIEW

Libtayo, a programmed death receptor-1 (PD-1) blocking antibody, is indicated for the treatment of patients for the following uses:[1]

- **Cutaneous Squamous Cell Carcinoma (CSCC)**, metastatic or locally advanced disease, who are not candidates for surgery or curative radiation.
- **Basal Cell Carcinoma**, treatment of patients with locally advanced or metastatic disease, previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate.
- **Non-Small Cell Lung Cancer**, first-line treatment in patients with tumors that have high programmed death-ligand 1 (PD-L1) expression (tumor proportion score [TPS] ≥ 50%), as determined by an FDA-approved test, with no epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), or ROS1 aberrations. The disease can be locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or for metastatic disease.

GUIDELINES

- **Basal Cell Carcinoma:** According to the National Comprehensive Cancer Network (NCCN) guidelines on basal cell skin cancer (version 2.2021 – February 25, 2021), Libtayo is recommended for locally advanced or metastatic disease previously treated with a hedgehog pathway inhibitor or for whom such a therapy is not appropriate (category 2A).[2]
- **Cutaneous Squamous Cell Carcinoma:** According to the NCCN guidelines (version 2.2020 – July 14, 2020) on squamous cell carcinoma (SCC), the primary goals of treatment are the complete removal of the tumor and the maximal preservation of function and cosmesis.[3] Surgical excision offers the most effective and efficient means for curative therapy, but considerations of patient preference, preservation of function and cosmesis may lead to choosing radiation therapy as primary treatment to achieve optimal results. Libtayo is recommended as a "preferred" therapy (category 2A) for complicated cases of locally advanced disease in which curative surgery and curative radiotherapy are not feasible; for regional disease if curative radiotherapy is not feasible; and also for regional recurrence or distant metastatic disease if surgery or radiotherapy are not feasible.
- **Non-Small Cell Lung Cancer:** The NCCN guidelines for non-small cell lung cancer (version 4.2021 – March 3, 2021) recommend Libtayo as one of the Preferred, category 1, treatment option for first-line therapy for programmed death ligand-1 (PD-L1) ≥ 50% and negative for actionable molecular markers.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Libtayo. Because of the specialized skills required for evaluation and diagnosis of patients treated with Libtayo as well as the monitoring required for adverse events and long-term efficacy, approval requires Libtayo to be prescribed by, or in consultation with, a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Libtayo is recommended in those who meet the following criteria:

FDA-Approved Indications

~~69.~~66. **Basal Cell Carcinoma.** Approve for 1 year if the patient meets ALL of the following criteria (A, B, and C):
- **A)** Patient has locally advanced or metastatic disease; AND
- **B)** Patient meets ONE of the following (i or ii):
  - **i.** Patient has received previous treatment with at least one hedgehog pathway inhibitor; OR
    Note: Examples are Erivedge (vismodegib capsules), Odomzo (sonidegib capsules).
  - **ii.** Hedgehog pathway inhibitor is not an appropriate therapy for patient; AND
    Note: Not appropriate due to intolerance or lack of efficacy.
- **C)** The medication is prescribed by or in consultation with an oncologist.

~~70.~~67. **Cutaneous Squamous Cell Carcinoma.** Approve for 1 year if the patient meets ALL of the following criteria (A, B, and C):
- **A)** Patient has locally advanced or metastatic disease; AND
- **B)** Patient is not a candidate for curative surgery or curative radiation; AND
- **C)** The medication is prescribed by or in consultation with an oncologist.

3. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets ALL of the following criteria (A, B, C, and D):
- **A)** Patient meets ONE of the following criteria (i or ii):
  - **i.** Patient has locally advanced disease and is not eligible for surgical resection or chemoradiation; OR
  - **ii.** Patient has metastatic disease; AND
- **B)** The tumor proportion score (TPS) for programmed death ligand-1 (PD-L1) as determined by an approved test is ≥ 50%; AND
- **C)** The tumor is negative for actionable mutations; AND
  Note: Examples include sensitizing epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, *RET* rearrangement positive, *MET* exon 14 skipping, *NTRK* gene fusion positive, *BRAF V600E* mutation-positive, and *ROS1* rearrangement positive.
- **D)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Libtayo is not recommended in the following situations:

275. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

344. Libtayo® injection for intravenous use [prescribing information]. Tarrytown, NY: Regeneron/Sanofi Genzyme; February 2021.
345. The NCCN Basal Cell Skin Cancer Clinical Practice Guidelines in Oncology (Version 2.2021 – February 25, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed March 3, 2021.
346. NCCN Squamous Cell Skin Cancer Clinical Practice Guidelines in Oncology (Version 2.2020 – July 14, 2020). ©2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 25, 2020.
347. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 4.2021 – March 3, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed March 3, 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/03/2018
Annual Revision	No criteria changes	10/02/2019
Annual Revision	**Cutaneous Squamous Cell Carcinoma:** Deleted abbreviation, CSCC, from indication and in criteria and replaced it with "disease".	10/28/2020
Selected Revision	**Basal Cell Carcinoma:** Added new condition and criteria based on FDA-approval. **Non-Small Cell Lung Cancer:** Added new condition and criteria based on FDA-approval.	03/03/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Lumoxiti Prior Authorization Policy

- Lumoxiti™ (moxetumomab pasudotox-tdfk injection for intravenous use - AstraZeneca)

REVIEW DATE: 09/23/2020

OVERVIEW

Lumoxiti, a CD22-directed cytotoxin, is indicated for the treatment of adult patients with relapsed or refractory hairy cell leukemia who received at least two prior systemic therapies, including treatment with a purine nucleoside analog.[1] Limitations of Use: Lumoxiti is not recommended for use in patients with a creatinine clearance ≤ 29 mL/min.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on Hairy Cell Leukemia (version 1.2020 – August 23, 2020) recommend purine nucleoside analogs (cladribine and/or pentostatin) as first-line agents for hairy cell leukemia.[2,3] Lumoxiti is recommended as a single agent for the treatment of progression of hairy cell leukemia after therapy for relapsed/refractory disease.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lumoxiti. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Lumoxiti as well as the monitoring required for adverse events and long-term efficacy, approval requires Lumoxiti to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lumoxiti is recommended in those who meet the following criteria:

FDA-Approved Indications

16. Hairy Cell Leukemia. Approve for 6 months if the patient meets the following criteria (A, B, C, and D):

M) Patient is ≥ 18 years of age; AND

N) Patient has received ≥ 2 prior systemic therapies, including therapy with a purine analog; AND
Note: Purine analogs include cladribine and pentostatin.

O) Patient has an estimated creatinine clearance ≥ 30 mL/min; AND

P) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lumoxiti is not recommended in the following situations:

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

603. Lumoxiti™ injection for intravenous use [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals; January 2019.
604. The NCCN Hairy Cell Leukemia Clinical Practice Guidelines in Oncology (Version 1.2020 – August 23, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed September 16, 2020.
605. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 16, 2020. Search term: moxetumomab.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/03/2018
Annual Revision	No criteria changes.	09/25/2019
Annual Revision	No criteria changes.	09/23/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Margenza Prior Authorization Policy

- Margenza™ (margetuximab injection for intravenous use – MacroGenics, Inc.)

REVIEW DATE: 02/10/2021

OVERVIEW

Margenza, in combination with chemotherapy, is indicated for the treatment of adult patients with metastatic human epidermal growth factor receptor 2 (**HER2)-positive breast cancer** who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) breast cancer guidelines (version 1.2021 – January 15, 2021) have not addressed Margenza.[2] The recommended therapies for HER2-positive disease are as follows: trastuzumab + Perjeta (pertuzumab injection for intravenous use) + docetaxel is category 1, preferred regimen; or trastuzumab + Perjeta + paclitaxel (category 2A, preferred). Other recommended regimens include: Tukysa (tucatinib tablets) + trastuzumab + capecitabine (category 1), Kadcyla (ado-trastuzumab emtansine for intravenous use) [category 1], Enhertu (fam-trastuzumab deruxtecan-nxki injection for intravenous use), trastuzumab + paclitaxel ± carboplatin, trastuzumab + vinorelbine, trastuzumab + capecitabine, lapatinib + capecitabine, trastuzumab + lapatinib, Nerlynx (neratinib tablets) + capecitabine, and trastuzumab + other agents. For hormone receptor-positive (HR+), HER2-positive disease, endocrine therapy options include aromatase inhibitor ± trastuzumab; aromatase inhibitor + trastuzumab ± lapatinib; fulvestrant ± trastuzumab, tamoxifen ± trastuzumab (all category 2A).

Safety

Margenza has Boxed Warning for left ventricular dysfunction and embryo-fetal toxicity.[1] Margenza may lead to reductions in left ventricular ejection fraction (LVEF); treatment should be discontinued for a confirmed clinically significant decrease in left ventricular function.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Margenza. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Margenza as well as the monitoring required for adverse events and long-term efficacy, approval requires Margenza to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Margenza is recommended in those who meet the following criteria:

FDA-Approved Indications

27. Breast Cancer. Approve for 1 year if the patient meets all of the following (A, B, C, D, E, and F):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has metastatic human epidermal growth factor receptor 2 (HER2)-positive disease; AND
- **C)** Patient has tried at least two prior anti-HER2 regimens; AND
  Note: Some examples of anti-HER2 regimens are Perjeta (pertuzumab injection for intravenous use) + trastuzumab + docetaxel, Perjeta + trastuzumab + paclitaxel; Tukysa (tucatinib tablets) + trastuzumab + capecitabine, Kadcyla (ado-trastuzumab emtansine for intravenous use), Enhertu (fam-trastuzumab deruxtecan-nxki injection for intravenous use), trastuzumab + capecitabine, trastuzumab + lapatinib.
- **D)** At least one of the prior anti-HER2 regimen was used for metastatic disease; AND
- **E)** The medication is used in combination with chemotherapy; AND
  Note: Examples of chemotherapy are capecitabine, eribulin, gemcitabine, vinorelbine.
- **F)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Margenza is not recommended in the following situations:

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

13. Margenza™ injection for intravenous use [prescribing information]. Rockville, MD: MacroGenics, Inc.; December 2020.
14. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 1.2021 – January 15, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 26, 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	02/10/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Monjuvi Prior Authorization Policy
- Monjuvi® (tafasitamab-cxix injection for intravenous use – MorphoSys US/Incyte)

REVIEW DATE: 08/05/2020

OVERVIEW

Monjuvi, a CD19-directed antibody-drug conjugate, is indicated in combination with Revlimid® (lenalidomide capsules) for adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant.[1] Monjuvi is administered as a weight-based intravenous infusion. It should be given in combination with Revlimid for a maximum of 12 cycles, then as monotherapy until disease progression or unacceptable toxicity. Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Guidelines

Monjuvi is not yet addressed in guidelines from the National Comprehensive Cancer Network (NCCN).[2] For second-line or subsequent treatment of relapsed or refractory DLBCL in patients ineligible for transplantation, preferred regimens recommended by NCCN (version 3.2020 – August 4, 2020) include GemOx (gemcitabine/oxaliplatin) ± rituximab and Polivy® (polatuzumab vedotin intravenous injection) ± bendamustine ± rituximab (after ≥ two prior therapies). A variety of other chemotherapy-based regimens ± rituximab are also included among the other recommended regimens. Xpovio® (selinexor tablets), a nuclear export inhibitor, is listed for third-line or subsequent use.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Monjuvi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Monjuvi as well as the monitoring required for adverse events and long-term efficacy, approval requires Monjuvi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Monjuvi is recommended in those who meet the following criteria:

FDA-Approved Indications

189. Diffuse Large B-Cell Lymphoma. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has been treated with at least one prior chemotherapy regimen; AND
- **C)** According to the prescriber, the patient is not eligible for autologous stem cell transplant; AND
- **D)** Patient meets one of the following (i or ii):
  - **i.** Monjuvi will be used in combination with Revlimid (lenalidomide capsules); OR
  - **ii.** Patient has already received 12 cycles of Monjuvi; AND
- **E)** The agent is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Monjuvi is not recommended in the following situations:

188. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

606. Monjuvi® intravenous infusion [prescribing information]. Boston, MA: Morphosus US/Incyte; July 2020.
607. The NCCN B-Cell Lymphoma Clinical Practice Guidelines in Oncology (Version 2.2020 – July 9, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 3, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/05/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Mylotarg Prior Authorization Policy

- Mylotarg™ (gemtuzumab ozogamicin for injection – Pfizer)

REVIEW DATE: 07/15/2020; selected revisions 07/29/2020

OVERVIEW

Mylotarg, an antibody-drug conjugate directed towards the CD33 antigen, is indicated for the treatment of:

- **CD33-positive acute myeloid leukemia (AML)**, newly diagnosed, in adults and pediatric patients ≥ 1 month of age; AND
- **CD33-positive AML**, relapsed or refractory, in adults and in pediatric patients ≥ 2 years of age.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for AML (version 3.2020 – December 23, 2019) recommend Mylotarg for induction therapy, post-remission therapy, and for relapsed/refractory CD33-positive AML.[2,3] Mylotarg can be used as a single agent or in combination with cytarabine and daunorubicin. The NCCN guidelines for AML also recommend Mylotarg in patients ≥ 18 years of age for induction and consolidation therapy for high-risk (white blood cell count > 10,000/µL) acute promyelocytic leukemia, and for relapsed disease. Mylotarg can be used in combination with tretinoin and/or arsenic trioxide.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Mylotarg. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Mylotarg as well as the monitoring required for adverse events and long-term efficacy, approval requires Mylotarg to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mylotarg is recommended in those who meet the following criteria:

FDA-Approved Indications

17. **Acute Myeloid Leukemia – Newly Diagnosed CD33-Positive.** Approve for 1 year if the patient meets the following criteria (A and B):
    - **F)** Patient is ≥ 1 month of age; AND
    - **G)** Mylotarg is prescribed by or in consultation with an oncologist.

18. **Acute Myeloid Leukemia – Relapsed or Refractory CD33-Positive.** Approve for 1 month if the patient meets the following criteria (A and B):
    A) Patient is ≥ 2 years of age; AND
    B) Mylotarg is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

19. **Acute Promyelocytic Leukemia – High Risk.** Approve for 6 months if the patient meets the following criteria (A, B, and C):
    A) Patient is ≥ 18 years of age; AND
    B) Patient has high risk disease, defined as white blood cell count > 10,000/mcL; AND
    C) Mylotarg is prescribed by or in consultation with an oncologist.

20. **Acute Promyelocytic Leukemia – First Relapse (Morphologic or Molecular).** Approve for 6 months if the patient meets the following criteria (A and B):
    A) Patient is ≥ 18 years of age; AND
    B) Mylotarg is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Mylotarg is not recommended in the following situations:

189. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

608. Mylotarg™ for intravenous infusion [prescribing information]. Philadelphia, PA: Pfizer; June 2020.
609. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (Version 3.2020 – December 23, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 7, 2020.
610. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 7, 2020. Search term: gemtuzumab.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/17/2019
Annual Revision	**Acute Myeloid Leukemia – Newly Diagnosed CD33-Positive**. Revised approval criteria down to ≥ 1 month of age.	07/15/2020
Selected Revision	**Acute Promyelocytic Leukemia – First Relapse (Morphologic or Molecular)**. Revised age criteria to ≥ 18 years of age.	07/29/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Oncaspar® (pegaspargase injection for intramuscular or intravenous use – Servier)

DATE REVIEWED: 06/03/2020

OVERVIEW

Oncaspar is a conjugate of *Escherichia coli*-derived L-asparaginase and monomethoxypolyethylene glycol (mPEG).[1] L-asparaginase catalyzes the breakdown of L-asparagine into aspartic acid and ammonia. Leukemia cells have a

deficiency of asparagine synthetase and rely on exogenous sources of L-asparagine for survival. Oncaspar depletes plasma L-asparagine levels leading to leukemia cell death.

Oncaspar is indicated as a component of a multi-agent chemotherapy regimen for:

- The first-line treatment of pediatric and adult patients with acute lymphoblastic leukemia (ALL), and
- The treatment of pediatric and adult ALL patients with hypersensitivity to native forms of L-asparaginase.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for ALL (version 1.2020 – January 15, 2020) and the NCCN guidelines for Pediatric ALL (version 2.2020 – November 25, 2019) recommend pegaspargase as a component of a multiagent chemotherapeutic regimen for induction/consolidation therapy for ALL, for induction therapy in Philadelphia chromosome-negative ALL in patients ≥ 65 years of age, for relapsed/refractory Philadelphia chromosome-negative ALL, and relapsed/refractory Philadelphia chromosome-positive ALL.[2,3,5]

The NCCN guidelines for T-cell lymphomas (version 1.2020 – January 6, 2020) recommend pegaspargase as a component of therapy for extranodal NK/T-cell lymphoma, nasal type and as an alternative induction regimen if no response or progressive disease after primary treatment for hepatosplenic gamma-delta T-cell lymphoma.[3,4]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Oncaspar. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Oncaspar as well as the monitoring required for adverse events and long-term efficacy, approval requires Oncaspar to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Oncaspar is recommended in those who meet the following criteria:

FDA-Approved Indications

190. Acute Lymphoblastic Leukemia. Approve for 1 year if Oncaspar is prescribed by or consultation with an oncologist.

Other Uses with Supportive Evidence

191. Extranodal NK/T-cell Lymphoma, Nasal Type. Approve for 1 year if Oncaspar is prescribed by or in consultation with an oncologist.

192. Hepatosplenic Gamma-Delta T-cell Lymphoma. Approve for 1 year if the patient meets the following criteria (A and B):

A) The patient had no response or progressive disease after primary treatment; AND

B) Oncaspar is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Oncaspar has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

190. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

611. Oncaspar® injection for intramuscular and intravenous use [prescribing information]. Boston, MA: Servier Pharmaceutics; August 2019.
612. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (Version 1.2020 – January 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 27, 2020.
613. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 27, 2020. Search term: pegaspargase.
614. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 1.2020 – January 6, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 27, 2020.
615. The NCCN Pediatric Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (Version 2.2020 – November 25, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 27, 2020.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	06/05/2019
Annual Revision	Extranodal NK/T-cell Lymphoma, Nasal Type: Removed "Oncaspar is used for one of the following (i, ii, or iii)" criteria. Added criteria for Hepatosplenic Gamma-Delta T-cell Lymphoma.	06/03/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Onivyde® (irinotecan liposome injection – Ipsen Biopharmaceuticals)

DATE REVIEWED: 04/22/2020

OVERVIEW

Onivyde is a topoisomerase 1 inhibitor formulated into a liposomal dispersion for intravenous (IV) use.[1] Topoisomerase 1 inhibitors prevent the repair of breaks in single-strands of DNA, eventually leading to double-strand damage to DNA and cell death.

Onivyde is indicated, in combination with fluorouracil and leucovorin, for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.[1] Limitation of use: Onivyde is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.

Guidelines

The National Comprehensive Cancer Network (NCCN) Pancreatic Adenocarcinoma practice guidelines (Version 1.2020 – November 26, 2019) recommend Onivyde, in combination with fluorouracil and leucovorin, for the second-line treatment of locally advanced, or metastatic pancreatic adenocarcinoma in patients with Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.[2,3]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Onivyde. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with

Onivyde as well as the monitoring required for adverse events and long-term efficacy, approval requires Onivyde to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Onivyde is recommended in those who meet the following criteria:

FDA-Approved Indications

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193. Pancreatic Adenocarcinoma, Locally Advanced or Metastatic. Approve for 1 year if the patient meets the following criteria (A, B, and C):

- **A)** Patient has tried at least one chemotherapy regimen for pancreatic adenocarcinoma, either gemcitabine-based chemotherapy, or fluoropyrimidine-based chemotherapy without irinotecan; AND
- **B)** Onivyde will be used in combination with fluorouracil and leucovorin; AND
- **C)** Onivyde is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Onivyde has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

191. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

616. Onivyde® liposome injection [prescribing information]. Basking Ridge, NJ: Ipsen Biopharmaceuticals; June 2017.
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618. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on April 17, 2020. Search term: irinotecan liposome.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/24/2019
Annual Revision	No criteria change.	04/22/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Opdivo Prior Authorization Policy

- Opdivo® (nivolumab injection for intravenous use – Bristol-Myers Squibb)

REVIEW DATE: 01/13/2021

OVERVIEW

Opdivo, a human programmed death receptor-1 (PD-1) blocking antibody, is indicated for the treatment of the following:[1]

- **Classical Hodgkin lymphoma**, for adults that have relapsed or progressed after* autologous hematopoietic stem cell transplantation (auto-HSCT) and Adcetris® (brentuximab vedotin intravenous injection) OR three or more lines of systemic therapy that includes auto-HSCT.
- **Colorectal cancer**, with or without Yervoy for patients ≥ 12 years of age with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic disease that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.*
- **Esophageal squamous cell carcinoma**, for patients with unresectable advanced, recurrent, or metastatic disease after prior fluoropyrimidine- and platinum-based chemotherapy.
- **Head and neck squamous cell carcinoma**, in patients with recurrent or metastatic disease with disease progression on or after platinum-based therapy.
- **Hepatocellular carcinoma** (HCC), in patients who have been previously treated with Nexavar® (sorafenib tablets), with or without Yervoy.*
- **Malignant pleural mesothelioma:**
  - First-line treatment, in combination with Yervoy (ipilimumab intravenous injection) of adult patients with unresectable disease.
- **Melanoma**, in patients with:
  - Unresectable or metastatic disease as a single agent, OR
  - Unresectable or metastatic disease in combination with Yervoy® (ipilimumab intravenous injection) in patients with melanoma;** AND
  - Adjuvant treatment for lymph node involvement or metastatic disease who have undergone complete resection.
- **Non-small cell lung cancer**:
  - As first-line treatment in combination with Yervoy, in adults with metastatic disease expressing programed death-ligand 1 (≥ 1%) as determined by an FDA-approved test, without epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations; AND
  - As first-line treatment in combination with Yervoy and two cycles of platinum-doublet chemotherapy, in adults with recurrent or metastatic disease without *EGFR* or *ALK* genomic tumor aberrations; AND
  - Patients with metastatic disease and progression on or after platinum-based chemotherapy. Patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Opdivo.
- **Renal cell carcinoma** (RCC):
  - Patients with advanced disease who have received prior anti-angiogenic therapy; AND
  - In combination with Yervoy, for patients with intermediate or poor risk and previously untreated advanced RCC.
- **Urothelial carcinoma**, in patients with advanced or metastatic disease who:*
  - Have disease progression during or following platinum-containing chemotherapy; OR
  - Who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

* This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

** This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Opdivo. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Opdivo as well as the monitoring required for adverse events and long-term efficacy, approval requires the medication to be prescribed by or in consultation with a prescriber who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Opdivo is recommended in those who meet the following criteria:

FDA-Approved Indications

7. **Classic Hodgkin Lymphoma (cHL).** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets one of the following conditions (i, ii, or iii):[2]
     - **i.** Patient has had a hematopoietic stem cell transplantation (HSCT); OR
     - **ii.** Patient has tried three or more systemic regimens AND this includes an auto-HSCT as one line of therapy; OR
       Note: Examples are ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), Sanford V (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone), escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone).
     - **iii.** Patient is not eligible for transplant according to the prescriber; AND
   - **C)** The medication is prescribed by or in consultation with an oncologist.

     Note: For pediatric patients, see **Pediatric Hodgkin Lymphoma** criteria.

8. **Colon or Rectal Cancer, Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR).** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient is ≥ 12 years of age; AND
   - **B)** Patient meets one of the following (i or ii):
     - **i.** Patient has tried chemotherapy; OR
       Note: Examples of chemotherapy are fluoropyrimidine such as 5-fluorouracil (5-FU), capecitabine; oxaliplatin, irinotecan, or an adjunctive chemotherapy regimen such as FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).
     - **ii.** Patient has unresectable or metastatic disease and is not a candidate for intensive therapy, according to the prescriber; AND
   - **C)** The medication is prescribed by or in consultation with an oncologist.

9. **Esophageal Squamous Cell Carcinoma.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   - **A)** Patient has tried fluoropyrimidine- and platinum-based chemotherapy; AND
     Note: Examples of fluoropyrimidines are 5-fluorouracil (5-FU) and capecitabine. Examples of platinum medications are cisplatin, carboplatin, and oxaliplatin.
   - **B)** The medication is prescribed by or in consultation with an oncologist.

10. **Head and Neck Squamous Cell Carcinoma.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):

A) Patient has non-nasopharyngeal disease; AND
B) Patient meets ONE of the following conditions (i or ii):
  i. Patient has tried chemotherapy; OR
  Note: Examples of chemotherapy are cisplatin, carboplatin**,** Erbitux® (cetuximab intravenous infusion), 5-fluorouracil (5-FU), capecitabine, paclitaxel, docetaxel, methotrexate (MTX).
  ii. A platinum-containing chemotherapy regimen or other chemotherapy is contraindicated, according to the prescriber; AND
C) The medication is prescribed by or in consultation with an oncologist.

11. Hepatocellular Carcinoma, Including Hepatobiliary Cancers. Approve for 1 year if the patient meets BOTH of the following (A and B):
G) Patient has tried at least one tyrosine kinase inhibitor (TKI); AND
Note: Examples are Nexavar (sorafenib tablets), Lenvima (levatinib capsules).
H) The medication is prescribed by or in consultation with an oncologist.

12. Malignant Pleural Mesothelioma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has unresectable disease; AND
C) The medication is used in combination with Yervoy (ipilimumab for injection); AND
D) The medication is prescribed by or in consultation with an oncologist.

13. Melanoma Approve for the duration noted if the patient meets BOTH of the following (A and B):
Note: This includes cutaneous melanoma, brain metastases due to melanoma, and uveal melanoma.
A) Patient meets ONE of the following (i or ii):
  i. Approve for 1 year if the patient has unresectable, advanced, or metastatic melanoma; OR
  ii. Approve for up to 1 year of treatment (total) if Opdivo will be used as adjuvant treatment; AND
  Note: Examples are in a patient with no evidence of disease following resection of node-positive disease, locoregional recurrence, or in-transit recurrence.
B) The medication is prescribed by or in consultation with an oncologist.

14. Non-Small Cell Lung Cancer (NSCLC). Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has advanced or metastatic disease; AND
C) Patient meets one of the following (i, ii, or iii):
  i. Opdivo is used as first-line therapy and the patient meets all of the following (a, b, and c):
    a) The tumor expresses programmed death-ligand 1 (PD-L1) ≥ 1% as determined by an FDA-approved test; AND
    b) Opdivo will be used in combination with Yervoy® (ipilimumab intravenous injection); AND
    c) The tumor is negative for actionable mutations; OR
    Note: Examples of actionable mutations include sensitizing epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, *NTRK* gene fusion-positive, *ROS1, BRAF V600E, MET 14* skipping mutation, *RET* rearrangement.
  ii. Opdivo is used as first-line therapy and the patient meets BOTH of the following (a and b):
  Note: This is regardless of PD-L1 status.
    a) The tumor is negative for actionable mutations; AND
    Note: Examples of actionable mutations include sensitizing epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, *NTRK* gene fusion-positive, *ROS1, BRAF V600E, MET 14* skipping mutation, *RET* rearrangement.

b) The medication will be used in combination with Yervoy (ipilimumab intravenous injection) AND platinum-doublet chemotherapy; OR
Note: Examples of platinum-doublet chemotherapy are carboplatin or cisplatin with Alimta (pemetrexed for injection), carboplatin and paclitaxel.

iii. Opdivo is used as subsequent therapy and the patient meets all of the following (a, b, and c):

a) Patient has tried systemic chemotherapy; AND
Note: Examples of systemic chemotherapy include cisplatin, carboplatin, Alimta (pemetrexed injection], Abraxane (paclitaxel albumin-bound injection), gemcitabine, paclitaxel.

b) Patient has not progressed on prior therapy with a programmed death-1 (PD-1)/PD-ligand 1 (PD-L1) inhibitor; AND
Note: This includes previous therapy with either one of Opdivo, Keytruda (pembrolizumab for injection), or Tecentriq (atezolizumab for injection).

c) If the tumor is positive for an actionable mutation, the patient has received targeted drug therapy for the specific mutation.
Note: Examples of actionable mutations include sensitizing epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, *NTRK* gene fusion-positive, *ROS1*, *BRAF V600E, MET 14* skipping mutation, *RET* rearrangement; AND

D) The medication is prescribed by or in consultation with an oncologist.

15. Renal Cell Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):

A) Patient has advanced (e.g., relapsed, Stage IV, or metastatic) disease; AND

B) If used as first-line therapy, the medication is used in combination with Yervoy (ipilimumab for injection); AND

C) The medication is prescribed by or in consultation with an oncologist.

16. Urothelial Carcinoma. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient has tried at least one other chemotherapy regimen; AND
Note: Examples of chemotherapy regimens are cisplatin, carboplatin, gemcitabine, Keytruda (pembrolizumab intravenous infusion), Tecentriq (atezolizumab intravenous infusion).

B) The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

17. Anal Carcinoma. Approve for 1 year if the patient meets BOTH of the following (A and B):

C) Patient has received other chemotherapy; AND
Note: Examples of chemotherapy are 5-fluorouracil (5-FU), cisplatin, carboplatin plus paclitaxel, FOLFOX (oxaliplatin, leucovorin, and 5-FU).

D) The medication is prescribed by or in consultation with an oncologist.

18. Endometrial Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):

A) Patient has progressed on at least one prior systemic therapy; AND
Note: Examples are carboplatin, paclitaxel, docetaxel, cisplatin, doxorubicin, topotecan, ifosfamide, everolimus/letrozole.

B) Patient has mismatch repair deficient (dMMR) disease; AND

C) The medication is prescribed by or in consultation with an oncologist.

19. Extranodal NK/T-Cell Lymphoma, Nasal Type. Approve for 1 year if the patient meets ALL of the following (A and B):

A) Patient has received an asparaginase-based chemotherapy regimen; AND
Note: Examples of asparaginase-based chemotherapy are dexamethasone, ifosfamide, pegaspargase, etoposide; and gemcitabine, pegaspargase, oxaliplatin.
B) The medication is prescribed by or in consultation with an oncologist.

20. Gastric Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) The disease is negative for human epidermal growth factor receptor 2 (HER2) overexpression; AND
B) The tumor expression for programmed death ligand-1 (PD-L1) has a combined positive score (CPS) ≥ 5; AND
C) The medication is used in combination with fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin; AND
D) The medication is prescribed by or in consultation with an oncologist.

21. Gestational Trophoblastic Neoplasia. Approve for 1 year if the patient meets BOTH of the following (A and B):
A) Patient meets one of the following (i or ii):
i. Patient has tried at least one previous chemotherapy regimen for recurrent or progressive disease; OR
Note: Examples of chemotherapy regimens contain etoposide, cisplatin/carboplatin, paclitaxel, bleomycin, ifosfamide, methotrexate.
ii. Patient has methotrexate-resistant high-risk disease; AND
B) The medication is prescribed by or in consultation with an oncologist.

22. Merkel Cell Carcinoma. Approve for 1 year if the patient meets BOTH of the following (A and B):
A) Patient has disseminated Merkel cell carcinoma; AND
B) The medication is prescribed by or in consultation with an oncologist.

23. Pediatric Hodgkin Lymphoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is < 18 years of age; AND
B) Patient has tried at least one prior systemic chemotherapy; AND
Note: Examples are AVPC (doxorubicin, vincristine, prednisone, cyclophosphamide), ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide), OEPA (vincristine, etoposide, prednisone, doxorubicin).
C) If used for re-induction therapy, the medication is used in combination with Adcetris (brentuximab vedotin); AND
D) The medication is prescribed by or in consultation with an oncologist.

24. Small Bowel Adenocarcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
A) Patient has advanced or metastatic disease that is deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H); AND
B) Patient meets one of the following criteria (i or ii):
i. If the medication is used as initial therapy, the patient has tried oxaliplatin in the adjuvant setting or has a contraindication to oxaliplatin; OR
ii. The medication will be used as subsequent therapy; AND
C) The medication is prescribed by or in consultation with an oncologist.

19. Vulvar Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
A) Patient has human papilloma virus (HPV)-related disease; AND

B) Patient has tried at least one prior systemic therapy; AND
Note: Examples are cisplatin, carboplatin, fluorouracil, paclitaxel, bevacizumab.
C) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Opdivo is not recommended in the following situations:

276. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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45. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (Version 6.2020 – July 16, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 11, 2021.
46. The NCCN Anal Carcinoma Clinical Practice Guidelines in Oncology (Version 2.2020 – May 6, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 11, 2021.
47. The NCCN Gestational Trophoblastic Neoplasia Cancer Clinical Practice Guidelines in Oncology (Version 3.2020 – October 6, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 11, 2021.
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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	New criteria	12/18/2019
Selected Revision	**Non-Small Cell Lung Cancer:** Added criteria for use of Opdivo as first-line therapy. **Extranodal NK/T-Cell Lymphoma, Nasal Type:** Added new approval condition and criteria.	06/24/2020
Annual Revision	**Classic Hodgkin Lymphoma:** Added age requirement of at least 18 years since indication is in adults. Added Note referring to Pediatric Hodgkin Lymphoma indication for pediatric patients. **Endometrial Carcinoma:** Added new approval condition and criteria based on guidelines. **Gastric Cancer:** Added new approval condition and criteria based on guidelines/compendium. **Malignant Pleural Mesothelioma:** Moved to FDA-approved uses. Modified criteria and deleted requirement of prior therapy since it is approved for first-line use. Added age requirement for adults, criteria for use in combination with Yervoy, and disease is unresectable. **Non-Small Cell Lung Cancer:** Added age requirement of at least 18 years since indication is in adults. Added new criteria based on FDA-approval for use in combination with Yervoy and platinum-doublet chemotherapy and no actionable mutations. In subsequent therapy criteria, deleted specification of nonsquamous cell NSCLC. In reference to mutations, changed verbiage from "targetable" mutations to "actionable" mutations. Added *NTRK* gene fusion-positive to list of examples of actionable mutations and specified *BRAF* as *V600E* mutation. **Pediatric Hodgkin Lymphoma:** Added criteria and approval condition based on guidelines. **Renal Cell Carcinoma:** Added criteria that if medication is used first-line, it is used in combination with Yervoy. **Small Cell Lung Cancer:** Removed approval condition and criteria since FDA-approval for this indication has been rescinded since confirmatory trials did not meet overall survival endpoint. **Vulvar Cancer:** Added new approval condition and criteria based on guidelines.	01/13/2021

NSCLC – Non-small cell lung cancer.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Padcev Prior Authorization Policy

- Padcev™ (enfortumab vedotin – ejfv injection for intravenous use – Astellas Pharma and Seattle Genetics)

REVIEW DATE: 12/16/2020

OVERVIEW

Padcev, an antibody-drug conjugate, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) **bladder cancer** clinical practice guidelines (version 6.2020 – July 16, 2020) recommend Padcev for the subsequent treatment of locally advanced or metastatic urothelial carcinoma of the bladder, upper genitourinary tract, prostate, and urethra.[2,3] Patients should have previously received platinum-containing chemotherapy and a checkpoint inhibitor, if eligible.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Padcev. All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Padcev as well as the monitoring required for adverse events and long-term efficacy, approval requires Padcev to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Padcev is recommended in those who meet the following criteria:

FDA-Approved Indications

194. Urothelial Carcinoma. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):

- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has locally advanced or metastatic disease; AND
- **C)** Patient has previously received a programmed death receptor-1 or programmed death-ligand 1 inhibitor (checkpoint inhibitor), unless the prescriber determines the patient is not eligible for checkpoint inhibitor therapy; AND
  Note: Programmed death receptor-1 and programmed death-ligand 1 inhibitors include: Opdivo® (nivolumab injection), Keytruda® (pembrolizumab injection), Tecentriq® (atezolizumab injection), Bavencio® (avelumab injection), and Imfimzi® (durvalumab injection).
- **D)** Patient has previously received platinum-containing chemotherapy, unless the prescriber determines the patient is not eligible for platinum chemotherapy; AND
  Note: Examples include cisplatin, carboplatin, and oxaliplatin.
- **E)** Padcev is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Padcev is not recommended in the following situations:

192. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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620. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (version 6.2020 – July 16, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 10, 2020.
621. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 10, 2020. Search term: enfortumab.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/20/2019
Selected Revision	Revised criteria for a patient who previously received a programmed death receptor-1 or programmed death-ligand 1 inhibitor to include: unless the prescriber determines the patient is not eligible for checkpoint inhibitor therapy. Revised criteria for a patient who previously received platinum-containing chemotherapy to include: unless the prescriber determines the patient is not eligible for platinum chemotherapy.	01/29/2020

Annual Revision	No criteria changes.	12/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Pepaxto Utilization Review Medical Policy
- Pepaxto® (melphalan flufenamide intravenous infusion – Oncopeptides)

REVIEW DATE: 03/10/2021

OVERVIEW
Pepaxto, an alkylating drug, is indicated in combination with dexamethasone, for treatment of adults with relapsed or refractory **multiple myeloma**, who have received at least four prior lines of therapy, and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody. Pepaxto is not recommended for use as a conditioning regimen for transplant.

Guidelines
Pepaxto is not addressed in current guidelines from the National Comprehensive Cancer Network (NCCN).[2] NCCN guidelines for multiple myeloma (version 4.2021 – December 10, 2020) address the diagnosis, treatment, and follow-up for patients with multiple myeloma.[2,3] Although Pepaxto is not addressed, other formulations of melphalan (melphalan, melphalan hydrochloride) are addressed in the guidelines. For non-transplant candidates, melphalan in combination with Darzalex/bortezomib/prednisone is among the regimens for primary therapy.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Pepaxto. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Pepaxto as well as the monitoring required for adverse events and long-term efficacy, approval requires Pepaxto to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Pepaxto is recommended in those who meet one of the following criteria:

FDA-Approved Indications

21. Multiple Myeloma. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
- **18.** Patient is ≥ 18 years of age; AND
- **19.** The medication will be used in combination with dexamethasone; AND
- **20.** Patient has tried at least four regimens for multiple myeloma; AND
- **21.** Among the previous therapies tried, the patient has received at least one drug from each of the following classes (i, ii, and iii):
  - **i.** Proteasome inhibitor; AND
    Note: Examples include Velcade (bortezomib injection), Kyprolis (carfilzomib infusion), Ninlaro (ixazomib capsules).
  - **ii.** Immunomodulatory drug; AND
    Note: Examples include Revlimid (lenalidomide capsules), Pomalyst (pomalidomide capsules), Thalomid (thalidomide capsules).
  - **iii.** Anti-CD38 monoclonal antibody; AND

Note: For example, Darzalex (daratumumab infusion), Darzalex Faspro (daratumumab and hyaluronidase-fihj subcutaneous injection), or Sarclisa (isatuximab-irfc infusion).

22. The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Pepaxto is not recommended in the following situations:

193. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

24. Pepaxto [prescribing information]. Waltham, MA: Oncopeptides; February 2020.
25. The NCCN Drugs and Biologics Compendium. © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 4, 2021. Search term: Papexto, melphalan.
26. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (Version 3.2020 – March 10, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 18, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New policy	--	03/10/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Perjeta Prior Authorization Policy

- Perjeta® (pertuzumab injection, for intravenous use – Roche/Genentech)

REVIEW DATE: 07/29/2020

OVERVIEW

Perjeta, a human epidermal growth factor receptor 2 (HER2) antagonist, is indicated for the treatment of HER2-positive breast cancer for the following uses:[1]

- **Neoadjuvant treatment,** of patients with locally advanced, inflammatory, or early stage disease (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer, in combination with trastuzumab and chemotherapy.
- **Adjuvant treatment,** of patients with early disease at high risk of recurrence, in combination with trastuzumab and chemotherapy.
- **Metastatic disease,** in combination with trastuzumab and docetaxel in patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

Guidelines

The National Comprehensive Cancer Network (NCCN) breast cancer guidelines (version 5.2020 – July 15, 2020) and Compendium has the following recommendations.[2,3] For preoperative (neoadjuvant)/adjuvant therapy in HER2-positive disease, doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab and Perjeta is one of the preferred regimens (category 2A). Docetaxel/carboplatin/trastuzumab/Perjeta is another recommend regimen (category 2A). Under other recommended regimens, doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab + Perjeta is also listed (category 2A). In the neoadjuvant/adjuvant setting, the chemotherapy agents in combination with trastuzumab + Perjeta are administered for usually four cycles, followed by trastuzumab ± Perjeta to complete 1 year of therapy.

In the metastatic setting, the preferred regimens are Perjeta + trastuzumab + docetaxel (category 1) or Perjeta + trastuzumab + paclitaxel (category 2A). In this setting, chemotherapy + trastuzumab + Perjeta is continued until disease progression or unmanageable toxicity.

The NCCN guidelines and compendium recommends use of Perjeta in combination with trastuzumab in patients with HER2-amplified, *RAS* and *BRAF* wild-type, colon and rectal cancer.[3-5] Perjeta is recommended for use in a variety of therapy settings (e.g., adjuvant therapy, primary treatment, subsequent therapy) in combination with trastuzumab, in patients who are not appropriate for intensive therapy and with no previous treatment with a HER2 inhibitor. It is category 2A recommended for primary and subsequent therapy settings; category 2B recommended for adjuvant therapy.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Perjeta. All approvals are provided for the duration noted below. Because of the specialized skills required for the evaluation and diagnosis of patients treated with Perjeta, as well as the monitoring required for the adverse events and long-term efficacy, approval requires Perjeta to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Perjeta is recommended in those who meet the following criteria:

FDA-Approved Indications

28. Breast Cancer – Neoadjuvant or Adjuvant Therapy. Approve for 1 year (total) if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
- **B)** Patient meets ONE of the following criteria (i or ii):
  - **i.** The medication will be used in combination with chemotherapy; OR
    Note: Examples include docetaxel, paclitaxel.
  - **ii.** The medication is continued after chemotherapy to complete 1 year of neoadjuvant or adjuvant therapy; AND
- **C)** Perjeta will be used in combination with a trastuzumab product; AND
- **D)** The medication is prescribed by or in consultation with an oncologist.

2. Breast Cancer – Metastatic Disease. Approve for 1 year if the patient meets all of the following (A, B, C, and D):
- **A)** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
- **B)** Patient has not been previously treated with anti-HER2 therapy or chemotherapy for metastatic disease; AND
- **C)** The medication will be used in combination with trastuzumab and chemotherapy; AND
  Note: Examples of chemotherapy are docetaxel, paclitaxel.
- **D)** The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

3. Colon or Rectal Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND

B) The medication is used in combination with trastuzumab; AND
C) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Perjeta is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

439. Perjeta® injection, for intravenous use [prescribing information]. South San Francisco, CA: Genentech, Inc.; January 2020.
440. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 5.2020 – July 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed July 27, 2020.
441. The NCCN Drugs & Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 27, 2020. Search term: pertuzumab.
442. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 4.2020 – June 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed July 27, 2020.
443. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (Version 6.2020 – June 25, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed July 27, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	No criteria changes	06/27/2018
Annual revision	Added new criteria for use in metastatic, adjuvant, and neoadjuvant therapy based on approved indications and guidelines. Criteria are matched with Perjeta medical policy.	07/10/2019
Annual revision	• **Breast Cancer – Neoadjuvant or Adjuvant Therapy**. Separated out indication from metastatic disease. Deleted criteria requiring locally advanced, inflammatory, or early stage disease for neoadjuvant therapy. For adjuvant therapy, deleted criteria requiring "early breast cancer with high risk of recurrence (e.g., node positive), according to the prescriber AND will be used in combination with chemotherapy." Instead, the following criteria was added: "The medication is continued after chemotherapy to complete 1 year of neoadjuvant or adjuvant therapy." • **Breast Cancer – Metastatic Disease**. Added separate indication for metastatic disease; previously it was addressed along with neoadjuvant/adjuvant therapy. Added criteria that the patient was not previously treated with anti-HER2 therapy or chemotherapy for metastatic disease, based on FDA label. Also, added requirement for combination use with chemotherapy along with trastuzumab. • **Colon or Rectal Cancer.** Added new approval condition under "Other Uses with Supportive Evidence" based on guideline recommendation.	07/29/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Phesgo Prior Authorization Policy

- Phesgo™ (pertuzumab, trastuzumab, and hyaluronidase-zzxf injection for subcutaneous use – Genentech, Inc.)

REVIEW DATE: 07/08/2020

OVERVIEW

Phesgo, a combination of pertuzumab, trastuzumab, and hyaluronidase-zzxf, is indicated for the following uses:[1]

- **Early breast cancer**, for use in combination with chemotherapy for the neoadjuvant treatment of adult patients with human epidermal growth factor receptor 2 (HER2)-positive, locally advanced, inflammatory, or early stage breast cancer (either > 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer. It is also indicated for the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence.
- **Metastatic breast cancer**, for use in combination with docetaxel for the treatment of adult patients with HER2-positive disease who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

Patients should be selected for therapy based on an FDA-approved companion diagnostic test.

Guidelines

The National Comprehensive Cancer Network (NCCN) breast cancer guidelines (version 5.2020 – July 15, 2020) notes that Phesgo may be substituted anywhere that the combination of Perjeta IV and trastuzumab IV are given as part of systemic therapy.[2] The guidelines note that Phesgo has a different dosing and administration instructions compared with the IV products. For preoperative (neoadjuvant)/adjuvant therapy in HER2-positive disease, doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab and Perjeta is one of the preferred regimens (category 2A). Docetaxel/carboplatin/trastuzumab/Perjeta is another recommend regimen (category 2A). Under other recommended regimens, doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab + Perjeta is also listed (category 2A). In the neoadjuvant/adjuvant setting, the chemotherapy agents in combination with trastuzumab + Perjeta are administered for usually four cycles, followed by trastuzumab ± Perjeta to complete 1 year of therapy. In the metastatic setting, the preferred regimens are Perjeta + trastuzumab + docetaxel (category 1) or Perjeta + trastuzumab + paclitaxel (category 2A). In this setting, chemotherapy + trastuzumab + Perjeta is continued until disease progression or unmanageable toxicity.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Phesgo. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Phesgo, as well as the monitoring required for adverse events and long-term efficacy, approval requires Phesgo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Phesgo is recommended in those who meet the following criteria:

FDA-Approved Indications

29. Breast Cancer – Neoadjuvant or Adjuvant Therapy. Approve for 1 year (total) if the patient meets all of the following (A, B, and C):
- **A)** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
- **B)** Patient meets one of the following criteria (i or ii):
  - **i.** The medication will be used in combination with chemotherapy; OR
    Note: Examples of chemotherapy are doxorubicin, cyclophosphamide, docetaxel, paclitaxel, carboplatin.
  - **ii.** Phesgo is continued after chemotherapy to complete 1 year of neoadjuvant or adjuvant therapy; AND
- **C)** The medication is prescribed by or in consultation with an oncologist.

2. Breast Cancer – Metastatic Disease. Approve for 1 year if the patient meets all of the following (A, B, C, and D):
- **A)** Patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
- **B)** Patient has not been previously treated with anti-HER2 therapy or chemotherapy for metastatic disease; AND
- **C)** The medication will be used in combination with chemotherapy; AND
  Note: Examples of chemotherapy are docetaxel, paclitaxel.
- **D)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Phesgo is not recommended in the following situations:

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

15. Phesgo™ injection for subcutaneous use [prescribing information]. South San Francisco, CA: Genentech, Inc.; June 2020.
16. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 5.2020 – July 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 20, 2020.

HISTORY

Type of Revision	Summary of Changes*	Review Date
New Policy	--	07/08/2020
Update	7/27/2020: updated guidelines with Phesgo.	--

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Polivy Prior Authorization Policy
- Polivy™ (polatuzumab vedotin – piiq injection for intravenous use – Genentech)

REVIEW DATE: 06/24/2020

OVERVIEW

Polivy, a CD79b-directed antibody-drug conjugate, is indicated in combination with bendamustine and a rituximab product is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, after at least two prior therapies.[1] Accelerated approval was granted for this indication based on complete response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on B-Cell Lymphomas (version 1.2020 – January 22, 2020) recommend Polivy for the second-line or subsequent treatment of DLBCL, follicular lymphoma, histologic transformation of nodal marginal zone lymphoma to DLBCL, mantle cell lymphoma, AIDS-related B-cell lymphoma, post-transplant lymphoproliferative disorders, and high-grade B-cell lymphoma after ≥ 2 prior therapies in non-candidates for transplant.[2,3]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Polivy. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Polivy as well as the monitoring required for adverse events and long-term efficacy, approval requires Polivy to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Polivy is recommended in those who meet the following criteria:

FDA-Approved Indications

195. Diffuse Large B-Cell Lymphoma. Approve for 6 months if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has been treated with at least two prior chemotherapy regimens; AND
- **C)** Polivy is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

196. B-Cell Lymphoma. (Note: Examples include follicular lymphoma, mantle cell lymphoma, high-grade B-cell lymphoma, AIDS-related B-cell lymphoma, post-transplant lymphoproliferative disorders, histologic transformation of nodal marginal zone lymphoma to diffuse large B-cell lymphoma). Approve for 6 months if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has been treated with at least two prior chemotherapy regimens; AND
- **C)** Polivy is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Polivy is not recommended in the following situations:

194. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

622. Polivy™ injection for intravenous use [prescribing information]. South San Francisco, CA: Genentech; June 2019.
623. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 1.2020 – January 22, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 16, 2020.
624. The NCCN Drugs & Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 16, 2020. Search term: polatuzumab.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	06/13/2019
Early annual revision	Diffuse Large B-Cell Lymphoma. Criterion was reworded to specify that two prior therapies was in fact two prior chemotherapy regimens. High-grade B-cell lymphoma was added to the Other Uses with Supportive Evidence section.	06/26/2019
Annual revision	**Diffuse Large B-Cell Lymphoma**. Removed criteria for used in combination with bendamustine and a rituximab product. **High-Grade B-cell Lymphoma**. Revised condition of approval to B-Cell Lymphoma and added a note with examples of B-cell lymphoma. Removed criteria for used in combination with bendamustine and a rituximab product.	06/24/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Portrazza Prior Authorization Policy

- Portrazza® (necitumumab injection for intravenous use – Eli Lilly)

REVIEW DATE: 01/20/2021

OVERVIEW

Portrazza is indicated in combination with gemcitabine and cisplatin for the **first-line treatment** of patients with **metastatic squamous non-small cell lung cancer** (NSCLC).[1] It has a limitation of use noted that it is not indicated for the treatment of non-squamous NSCLC.

Guidelines

The National Comprehensive Cancer Network (NCCN) NSCLC cancer guidelines (version 2.2021 – December 15, 2020) no longer addresses Portrazza in the treatment algorithms. In the discussion section, it is noted that the NCCN Panel feels the addition of Portrazza to treatment regimen is not beneficial based on toxicity, cost, and limited improvement in efficacy when compared with cisplatin/gemcitabine.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Portrazza. Because of the specialized skills required for evaluation and diagnosis of patients treated with Portrazza as well as the monitoring required for adverse events and long-term efficacy, approval requires the medication to be prescribed by or in consultation with a prescriber who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Portrazza is recommended in those who meet the following criteria:

FDA-Approved Indications

23. Non-Small Cell Lung Cancer (NSCLC). Approve for 1 year if the patient meets the following criteria (A, B, and C):

A) Patient has metastatic squamous NSCLC; AND

B) Portrazza will be used in combination with chemotherapy.
Note: Examples of chemotherapy are gemcitabine, cisplatin; AND

C) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Portrazza is not recommended in the following situations:

277. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

444. Portrazza® Intravenous Infusion [prescribing information]. Indianapolis, IN: Eli Lilly and Company; November 2015.
445. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 2.2021 – December 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 19, 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	New criteria	09/25/2019
Early Annual Revision	No criteria changes – early annual revision done to sync with medical policy revision date.	01/15/2020
Annual Revision	No criteria changes	01/20/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Poteligeo Prior Authorization Policy

- Poteligeo® (mogamulizumab-kpkc injection, for intravenous use – Kyowa Kirin, Inc.)

REVIEW DATE: 09/02/2020

OVERVIEW

Poteligeo is indicated for the treatment of adult patients with relapsed or refractory mycosis fungoides or Sézary syndrome after at least one prior systemic therapy.[1]

GUIDELINES

The National Comprehensive Cancer Network (NCCN) guidelines on Primary Cutaneous Lymphomas (version 2.2020 – April 10, 2020) recommend Poteligeo for primary treatment and for treatment of relapsed/refractory mycosis fungoides/Sezary syndrome.[2,3]

The NCCN guidelines on T-Cell Lymphomas (version 1.2020 – January 6, 2020) recommend Poteligeo as a single agent for the treatment of relapsed/refractory adult T-cell leukemia/lymphoma, acute or lymphoma subtypes.[3,4]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Poteligeo. All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Poteligeo as well as the monitoring required for adverse events and long-term efficacy, approval requires Poteligeo to be prescribed by, or in consultation with, a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Poteligeo is recommended in those who meet the following criteria:

FDA-Approved Indications

~~71.~~68. **Mycosis Fungoides/Sezary Syndrome.** Approve for 1 year if Poteligeo is prescribed by or in consultation with an oncologist or dermatologist.

Other Uses With Supportive Evidence

~~72.~~69. **Adult T-cell Leukemia/Lymphoma**. Approve for 1 year if the patient meets ALL of the following (A and B):

A) Patient has relapsed or refractory disease; AND

B) Poteligeo is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Poteligeo is not recommended in the following situations:

278. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

348. Poteligeo® injection [prescribing information]. Bedminster, NJ: Kyowa Kirin, Inc.; August 2018.
349. NCCN Primary Cutaneous Lymphomas Clinical Practice Guidelines in Oncology (Version 2.2020 – April 10, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 24, 2020.
350. NCCN Drugs & Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 24, 2020. Search terms: mogamulizumab-kpkc.
351. NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 1.2020 – January 6, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 24, 2020.

History

Type of Revision	Summary of Changes	Review Date
New Policy	--	09/05/2018
Selected Revision	Updated NCCN guidelines version to 5.2018. Added Adult T-cell leukemia/lymphoma (ATLL) as an approvable indication in the "Other uses with supporting evidence" section (included in the NCCN guidelines).	10/17/2018
Annual Revision	Combined mycosis fungoides and Sezary syndrome criteria into one indication and removed relapsed/refractory criteria and removed at least one prior systemic therapy criteria. Revised Adult T-cell leukemia/lymphoma criteria by removing CCR4 positive ATLL and removing dermatologist.	09/04/2019
Annual Revision	No criteria changes.	09/02/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Proleukin Prior Authorization Policy

- Proleukin® (aldesleukin injection for intravenous use – Prometheus Laboratories)

REVIEW DATE: 12/16/2020

OVERVIEW

Proleukin, a human recombinant interleukin-2 product, is indicated for the following conditions, in adults:

- **Metastatic melanoma**.
- **Metastatic renal cell carcinoma**.[1]

Guidelines

Proleukin is addressed in the following National Comprehensive Cancer Network (NCCN) guidelines:

- The NCCN **cutaneous melanoma** (version 1.2021 – November 25, 2020) NCCN clinical practice guidelines recommend Proleukin for unresectable or metastatic disease as a single agent for second-line or subsequent therapy for disease progression or after maximum clinical benefit from BRAF targeted therapy (Category 2A).[2,4] Proleukin may be considered for patients with small brain tumors and without significant peritumoral edema (Category 2B) or for intralesional therapy as primary or second-line treatment of unresectable stage III disease with clinical or satellite/in-transit metastases, or local satellite/in-transit recurrence (Category 2B).
- The NCCN **hematopoietic cell transplantation** (version 2.2020 – March 23, 2020) NCCN clinical practice guidelines recommend Proleukin as additional therapy, in combination with systemic corticosteroids, for steroid-refractory chronic graft-vs-host disease.[2,5]
- The NCCN **kidney cancer** (version 1.2021 – July 15, 2020) NCCN clinical practice guidelines recommend Proleukin as a single agent for first-line (Category 2A) and subsequent (Category 2B) therapy for patients with relapsed or stage IV disease and clear cell histology.[2,3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Proleukin. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Proleukin as well as the monitoring required for adverse events and long-term efficacy, approval requires Proleukin to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Proleukin is recommended in those who meet the following criteria:

FDA-Approved Indications

197. Cutaneous Melanoma. Approve for 6 months if the patient meets ONE of the following (A or B):

A) Intravenous Therapy. Approve if the patient meets the following criteria (i, ii, iii, iv, and v):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient has metastatic or unresectable disease; AND
- **iii.** Patient has tried at least one other systemic therapy; AND
- **iv.** Proleukin will be used as a single agent; AND
- **v.** Proleukin is prescriber by or in consultation with an oncologist.

B) Intralesional Therapy. Approve if the patient meets the following criteria (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Proleukin will be directly injected into metastatic, recurrent, or unresectable cutaneous, subcutaneous, or nodal lesions; AND
- **iii.** The medication is prescribed by or in consultation with an oncologist or dermatologist.

198. Kidney Cancer. Approve for 6 months if the patient meets the following criteria (A, B, C, D, and E):

A) Patient is ≥ 18 years of age; AND
B) Patient has relapsed or metastatic disease; AND
C) Patient has clear cell histology; AND
D) Proleukin will be used as a single agent; AND
E) Proleukin is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

199. Graft-Versus-Host Disease. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):

A) Patient has chronic graft-versus-host disease; AND
B) According to the prescriber, the patient has steroid-refractory disease; AND
C) Proleukin will be used in combination with systemic corticosteroids; AND
D) Proleukin will be prescribed by or in consultation with an oncologist or a physician associated with a transplant center.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Proleukin is not recommended in the following situations:

195. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

625. Proleukin® injection for intravenous use [prescribing information]. San Diego, CA: Prometheus Laboratories Inc.; August 2018.
626. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 10, 2020. Search term: aldesleukin.
627. The NCCN Kidney Cancer Clinical Practice Guidelines (Version 1.2021 – July 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 10, 2020.
628. The NCCN Cutaneous Melanoma Clinical Practice Guidelines (Version 1.2021 – November 25, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 10, 2020.
629. The NCCN Hematopoietic Cell Transplantation Clinical Practice Guidelines (Version 2.2020 – March 23, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 10, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/18/2019
Select revision	**Cutaneous Melanoma:** For Intralesional Therapy, a dermatologist was added to the list of specialist physicians.	01/15/2020
Annual Revision	No criteria changes.	12/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Rituxan Hycela Prior Authorization Policy

- Rituxan Hycela® (rituximab and hyaluronidase human injection for subcutaneous use – Biogen and Genentech/Roche)

REVIEW DATE: 11/04/2020

OVERVIEW

Rituxan Hycela, a combination of rituximab and hyaluronidase human, is indicated for treatment of adults with the following indications:

- **Diffuse large B-cell lymphoma**, in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or other anthracycline-based chemotherapy regimens in patients with previously untreated disease.
- **Chronic lymphocytic leukemia**, in combination with FC (fludarabine + cyclophosphamide) for previously treated and previously untreated disease.
- **Follicular lymphoma**, as a single agent for relapsed or refractory disease; in previously untreated disease in combination with first-line chemotherapy and, as single-agent maintenance therapy in patients achieving a complete or partial response to rituximab + chemotherapy; and as a single agent after first-line CVP (cyclophosphamide, vincristine, and prednisone) in non-progressing (including stable disease) disease.

Rituxan Hycela contains the identical molecular antibody of rituximab available in Rituxan intravenous, but hyaluronidase has been added to facilitate systemic delivery. Rituxan Hycela should be administered under the care of a healthcare professional with appropriate medical support to manage severe and potentially fatal reactions. The dose of Rituxan Hycela is fixed regardless of the patient's body surface area; dose reductions are not recommended. When given in combination with chemotherapy, reduce the dose of chemotherapeutic drugs to manage adverse events. Rituxan Hycela is not indicated for treatment of non-malignant conditions.

Guidelines

Rituximab features prominently in the National Comprehensive Cancer Network (NCCN) guidelines for multiple conditions. The following guidelines from NCCN have been updated to list Rituxan Hycela (noted as rituximab + hyaluronidase) in most clinical scenarios when the intravenous formulation is recommended, if the patient has received the first full dose with rituximab intravenous.

- **B-cell Lymphomas:** In the guidelines (version 4.2020 – August 13, 2020), rituximab included in multiple treatment regimens across the spectrum of disease.[2]
- **Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma:** Rituximab features prominently in the guidelines (version 1.2021 – September 28, 2020) and is included in multiple treatment regimens across the spectrum of disease.[3]
- **Hairy Cell Leukemia:** Guidelines (version 1.2021 – September 28, 2020) recommend rituximab in multiple regimens for relapsed/refractory disease, including in patients with progressive disease after relapsed/refractory therapy.[4]
- **Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma:** Guidelines (version 2.2020 – April 15, 2020) include rituximab in regimens across the spectrum of disease (primary therapy, previously treated disease, and maintenance).[5]

Safety

There is a higher risk of hypersensitivity and other acute reactions during the first infusion.[1] Therefore, all patients must receive at least one full dose of rituximab intravenous, which allows for management by slowing or stopping the infusion, before receiving Rituxan Hycela. Patients who are unable to complete one full intravenous infusion should continue to receive subsequent cycles with Rituxan intravenous and should not switch to Rituxan Hycela until a full intravenous dose is successfully administered. Safety is otherwise comparable to rituximab intravenous.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Rituxan Hycela. Because of the specialized skills required for evaluation and diagnosis of patients treated with Rituxan Hycela as well as the monitoring required for adverse events (AEs) and long-term efficacy, approval requires Rituxan Hycela to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indications

22. B-Cell Lymphoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
Note: Examples of B-cell lymphomas include Diffuse Large B-cell Lymphoma [DLBCL], Follicular Lymphoma, Acquired Immune Deficiency [AIDS]-Related B-Cell Lymphoma, Burkitt Lymphoma, Castleman's Disease, Marginal Zone Lymphoma [e.g., extranodal or MALT {gastric or nongastric}, nodal, or splenic marginal zone lymphoma], Primary Mediastinal Large B-Cell Lymphoma, Mantle Cell Lymphoma, Post-Transplant Lymphoproliferative Disorders, Gray Zone Lymphoma, Primary Cutaneous B-Cell Lymphoma).
- **A)** Patient has already received at least one full dose of rituximab intravenous; AND
- **B)** Rituxan Hycela is administered under the care of a healthcare professional; AND
- **C)** The medication is being prescribed by or in consultation with an oncologist.

23. Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
- **A)** Patient has already received at least one full dose of rituximab intravenous; AND
- **B)** Rituxan Hycela is administered under the care of a healthcare professional; AND
- **C)** The medication is being prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

24. Hairy Cell Leukemia. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
- **A)** Patient has relapsed/refractory hairy cell leukemia; AND
- **B)** Patient has already received at least one full dose of rituximab intravenous; AND
- **C)** Rituxan Hycela is administered under the care of a healthcare professional; AND
- **D)** The medication is prescribed by or in consultation with an oncologist.

25. Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
- **A)** Patient has already received at least one full dose of rituximab intravenous; AND
- **B)** Rituxan Hycela is administered under the care of a healthcare professional; AND
- **C)** The medication is being prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Rituxan Hycela is not recommended in the following situations:

279. Granulomatosis with Polyangiitis (Wegener's granulomatosis) or Microscopic Polyangiitis. Rituximab intravenous is indicated for treatment of these indications.[6] Rituxan Hycela has not been evaluated and does not have established dosing in this setting.

280. Pemphigus Vulgaris. Rituximab intravenous is indicated for treatment of pemphigus vulgaris.[6] Rituxan Hycela has not been evaluated and does not have established dosing for pemphigus vulgaris.

281. Rheumatoid Arthritis. Rituximab intravenous is indicated for treatment of RA.[6] Rituxan Hycela has not been evaluated and does not have established dosing for rheumatoid arthritis.

282. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

9. Rituxan Hycela™ injection for SC use [prescribing information]. South San Francisco, CA: Biogen and Genentech/Roche; May 2020.
10. The NCCN B-Cell Lymphoma Clinical Practice Guidelines in Oncology (Version 4.2020 – August 13, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 28, 2020.
11. The NCCN chronic lymphocytic leukemia/small lymphocytic lymphoma Clinical Practice Guidelines in Oncology (Version 1.2021 – September 28, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 28, 2020.
12. The NCCN Hairy Cell Leukemia Clinical Practice Guidelines in Oncology (version 1.2021 – September 28, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 28, 2020.
13. The NCCN Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma Clinical Practice Guidelines in Oncology (Version 1.2021 – September 1, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 28, 2020.
14. Rituxan® intravenous infusion [prescribing information]. South San Fransisco, CA: Genentech, Inc.; April 2019.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**B-Cell Lymphoma:** To align with NCCN recommendations, combine criteria for B-Cell Lymphomas and list follicular lymphoma and diffuse large B-cell lymphoma among examples of B-Cell Lymphomas (previously follicular lymphoma and diffuse large B-cell lymphoma were listed separately in the policy). **Chronic Lymphocytic Leukemia:** To align with NCCN guidelines, add Small Lymphocytic Lymphoma as an approvable condition with the same criteria as Chronic Lymphocytic Leukemia. Also, remove criterion that required Rituxan Hycela to be administered in combination with fludarabine and cyclophosphamide.	09/19/2018
Annual Revision	**Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma:** To align with other policies that approve for this condition, remove hematologist from the specialists who are required to prescribe or be consulted prior to approval. **B-Cell Lymphoma:** Primary cutaneous B-cell lymphoma was added to the list of examples of a B-cell lymphoma. To align with other policies that approve for this condition, remove hematologist from the specialists who are required to prescribe or be consulted prior to approval. **Hairy Cell Leukemia:** This indication was added to the policy as an Other Use with Supportive Evidence. Criteria approve for 1 year if the patient has relapsed or refractory disease and if the agent is prescribed by or in consultation with an oncologist. Similar to other indications, criteria also require that the patient has already received at least one dose of rituximab intravenous and that Rituxan Hycela will be administered under the care of a healthcare professional. **Conditions Not Recommended for Approval:** Pemphigus vulgaris was added as a condition not recommended for coverage.	10/16/2019
Annual Revision	**Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma:** This indication was added to the policy as an Other Use with Supportive Evidence. Criteria approve for 1 year if the medication is prescribed by or in consultation with an oncologist. Similar to other indications, criteria also require that the patient has already received at least one dose of rituximab intravenous and that Rituxan Hycela will be administered under the care of a healthcare professional.	11/04/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Romidepsin Products (Istodax)

- Istodax® (romidepsin injection for intravenous use – Celegene)
- Romidepsin injection for intravenous use – authorized generics – various

DATE REVIEWED: 06/03/2020

OVERVIEW

Romidepsin (Istodax, authorized generics) is a histone deacetylase (HDAC) inhibitor which catalyzes the removal of acetyl groups from acetylated lysine residues in histones resulting in gene expression modulation.[1] Romidepsin also catalyzes the removal of acetyl groups from non-histone proteins. In vitro, romidepsin induces cell cycle arrest and death due to the accumulation of acetylated histones.

Romidepsin is indicated for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy and for the treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) Primary Cutaneous Lymphomas practice guidelines (version 2.2020 – April 10, 2020) recommend romidepsin as systemic therapy for mycosis fungoides/Sezary syndrome with or without skin-directed therapy and as a single agent for relapsed or refractory primary cutaneous CD30+ T-cell lymphoproliferative disorders.[2,3]

The NCCN T-Cell Lymphomas practice guidelines (version 1.2020 – January 6, 2020) recommend romidepsin as a single agent for the second-line or subsequent therapy of relapsed or refractory peripheral T-cell lymphomas including anaplastic large cell lymphoma; peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma, enteropathy-associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, and nodal peripheral T-cell lymphoma with T-follicular helper (TFH) phenotype; follicular T-cell lymphoma; extranodal NK/T-cell lymphoma – nasal type; and hepatosplenic gamma-delta T-cell lymphoma.[3,4]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of romidepsin. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with romidepsin as well as the monitoring required for adverse events and long-term efficacy, approval requires romidepsin to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of romidepsin is recommended in those who meet the following criteria:

FDA-Approved Indications

200. T-Cell Lymphoma, Peripheral. Approve for 1 year if the patient meets the following (A, B, and C):
- **A)** The patient has relapsed or refractory disease; AND
- **B)** Romidepsin is used as a single agent; AND
- **C)** Romidepsin is prescribed by or in consultation with an oncologist.

201. Cutaneous T-Cell Lymphoma – Mycosis Fungoides/Sezary Syndrome. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** The patient has received at least one prior systemic therapy, AND
- **B)** Romidepsin is prescribed by or in consultation with an oncologist or dermatologist.

202. Cutaneous T-Cell Lymphoma – Cutaneous CD30+ T-Cell Lymphoproliferative Disorders. Approve for 1 year if the patient meets the following (A, B, C, and D):
- **A)** The patient has relapsed or refractory disease; AND
- **B)** The patient has one of the following diagnoses (i or ii):
  - **i.** Primary cutaneous anaplastic large cell lymphoma with multifocal lesions; OR
  - **ii.** Cutaneous anaplastic large cell lymphoma with regional nodes; AND
- **C)** Romidepsin is used as a single agent; AND
- **D)** Romidepsin is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

203. Extranodal NK/T-Cell Lymphoma, Nasal Type. Approve for 1 year if the patient meets the following (A, B, and C):
- **A)** The patient has relapsed/refractory disease following combination (asparaginase-based) chemotherapy; AND
- **B)** Romidepsin is used as a single agent; AND
- **C)** Romidepsin is prescribed by or in consultation with an oncologist.

204. Hepatosplenic Gamma-Delta T-Cell Lymphoma. Approve for 1 year if the patient meets the following (A, B, and C):

A) Romidepsin is used as subsequent therapy after two primary treatment regimens; AND

B) Romidepsin is used as a single agent; AND

C) Romidepsin is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Romidepsin has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

196. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

630. Istodax® injection for intravenous use. [prescribing information]. Summit, NJ: Celgene Corporation; November 2018.

631. The NCCN Primary Cutaneous Lymphomas Clinical Practice Guidelines in Oncology (Version 2.2020 – April 10, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 27, 2020.

632. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 27, 2020. Search term: romidepsin.

633. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 1.2020 – January 6, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed May 27, 2020.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	06/05/2019
DEU update 06/26/2019	Added authorized generics to policy. Changed Istodax to romidepsin in policy. Changed policy name to Oncology – Romidepsin Products (Istodax) PA Policy	Not applicable
Annual Revision	No change to criteria	06/03/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Sarclisa® (isatuximab-irfc injection, for intravenous use – Sanofi-Aventis)

DATE REVIEWED: 03/04/2020; selected revision 03/11/2020

OVERVIEW

Sarclisa, a CD38-directed monoclonal antibody, is indicated in combination with Pomalyst® (pomalidomide capsules) and dexamethasone for treatment of adults with multiple myeloma, for those who have received at least two previous therapies including with with Revlimid® (lenalidomide capsules) and a proteasome inhibitor.[1] In the pivotal study, the median number of prior lines of therapy was 3 lines (range, 2 to 11 prior lines of therapy). Safety and efficacy have not been established in patients < 18 years of age.

Disease Overview

Multiple myeloma is a cancer formed by malignant plasma cells which are found in the bone marrow.[2] Normally, B cells responding to an infection change into plasma cells that make antibodies to help attack and kill pathogens. In multiple myeloma, these plasma cells grow out of control and become cancerous. A monoclonal immunoglobulin (M protein) is produced by myeloma cells and may be found in the blood or excreted in the urine of patients with multiple myeloma. Beta-2 microglobulin is another protein made by myeloma cells, with high levels associated with more advanced disease. Sarclisa binds to CD38 and inhibits the growth of CD38-expressing tumor cells such as myeloma cells.

Guidelines

Sarclisa is not yet addressed in current guidelines for multiple myeloma.[3] Recently updated guidelines from the National Comprehensive Cancer Network (NCCN) [version 2.2020 – October 9, 2019] recommend various regimens as primary therapy (transplant eligible and non-transplant candidates), maintenance therapy, and previously-treated multiple myeloma. The relative efficacy and toxicity of each regimen, along with patient-specific factors (e.g., past therapies, renal disease), are considered for choice of primary and subsequent regimens.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Sarclisa. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Sarclisa as well as the monitoring required for adverse events and long-term efficacy, approval requires Sarclisa to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sarclisa is recommended in those who meet the following criteria:

FDA-Approved Indications

26. Multiple Myeloma. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, E and F):

24. The patient is ≥ 18 years of age; AND

25. The agent will be used in combination with Pomalyst (pomalidomide capsules)and dexamethasone; AND

26. The patient has tried at least TWO prior regimens for multiple myeloma.
Note: Examples include Velcade (bortezomib injection)/Revlimid (lenalidomide capsules) /dexamethasone, Kyprolis (carfilzomib infusion)/Revlimid/dexamethasone, Darzalex (daratumumab injection)/Velcade/melphalan/prednisone, Ninlaro (ixazomib capsules)/Revlimid/dexamethasone, and Darzalex/Revlimid/dexamethasone; AND

27. A proteasome inhibitor was a component of at least one previous regimen.
Note: Examples of proteasome inhibitors include Velcade (bortezomib injection), Kyprolis (carfilzomib infusion), Ninlaro (ixazomib capsules); AND

28. Revlimid (lenalidomide capsules) was a component of at least one previous regimen; AND

29. The agent is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Sarclisa has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

197. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

27. Sarclisa® injection [prescribing information]. Bridgewater, NJ: Sanofi-Aventis; March 2020.
28. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 2, 2020. Search term: isatuximab.
29. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (Version 2.2020 – October 9, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 2, 2020.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	03/04/2020
Selected revision	**Multiple myeloma:** Add the requirement that the patient must have tried at least two prior regimens, with criteria that specify a proteasome inhibitor and Revlimid must have been a component of at least one prior regimen. Previously criteria required a previous trial of a proteasome inhibitor and of an immunomodulatory drug, but did not specifically require Sarclisa to be in the third-line setting.	03/11/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Sylvant Prior Authorization Policy

- Sylvant® (siltuximab intravenous infusion – EUSA Pharma)

REVIEW DATE: 02/17/2021

OVERVIEW

Sylvant, an interleukin (IL)-6 antagonist, is indicated for treatment of patients with **multicentric Castleman's disease** (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative.[1] Because Sylvant did not bind to virally produced IL-6 in a nonclinical study, Sylvant has not been studied in patients with MCD who are HIV positive or HHV-8 positive. The pivotal trials showed a higher proportion of patients with durable tumor response (partial or complete response) and improvement in patient-reported outcomes (e.g., fatigue, physical function) with Sylvant vs. placebo. Patients were treated until treatment failure, defined as disease progression based on increased symptoms, radiologic progression, or deterioration in performance status. Safety and efficacy has not been established in patients < 18 years of age.

Disease Overview

MCD affects approximately 1,000 patients in the US. It typically presents with lymphoid hyperplasia at multiple sites, including the peripheral lymph nodes, bone marrow, and multiple organs. Patients often have serious infections, fevers, weight loss, fatigue, night sweats, and nerve damage that can cause weakness and numbness. Persistent IL-6 production has been implicated in the development of various autoimmune, chronic, inflammatory diseases and cancers, including MCD.[2] Sylvant, a human-mouse chimeric monoclonal antibody that is produced by Chinese hamster ovary cells, binds human IL-6 and prevents the binding of IL-6 to both soluble and membrane-bound IL-6 receptors.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for B-cell lymphomas (version 1.2021 – January 20, 2021) list Sylvant as a treatment option for MCD and for refractory or relapsed unicentric disease.[3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Sylvant. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Sylvant as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Sylvant to be prescribed by or in consultation with a physician who specializes in the condition being treated.

All reviews for use of Sylvant for COVID-19 and/or cytokine release syndrome associated with COVID-19 will be forwarded to the Medical Director.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sylvant is recommended in those who meet the following criteria:

FDA-Approved Indications

F) Castleman's Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

- **F)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following conditions (i, ii, iii, and iv):
  - **i.** Patient is ≥ 18 years of age; AND
  - **ii.** Patient is negative for the human immunodeficiency virus (HIV) and human herpesvirus-8 (HHV-8); AND
  - **iii.** Patient meets ONE of the following (a or b):
    - **a)** Patient has multicentric Castleman's disease; OR
    - **b)** Sylvant is being used for relapsed or refractory unicentric Castleman's disease; AND
  - **iv.** Sylvant is prescribed by or in consultation with an oncologist or hematologist.
- **B)** Patient is Currently Receiving Sylvant. Approve for 1 year if the patient has responded to Sylvant, as determined by the prescriber.

  Note: Examples of a response include stabilized disease, tumor response, and resolution or stabilization of symptoms, such as fatigue and physical function.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sylvant is not recommended in the following situations:

3. **COVID-19 (Coronavirus Disease 2019).** Forward all requests to the Medical Director.
   Note: This includes requests for cytokine release syndrome associated with COVID-19.

2. **Multiple Myeloma**. Efficacy is not established. In a Phase II study (n = 286) evaluating patients with relapsed or refractory multiple myeloma, median progression-free survival was similar in patients treated with Velcade (bortezomib injection) + Sylvant (8.0 months) vs. in those treated with Velcade + placebo (7.6 months).[4] Following 24.5 months of follow-up, there was not a significant difference between the groups in median overall survival (30.8 months in the group that received Velcade + Sylvant vs. 36.8 months in the Velcade + placebo group). There was not a significant difference on overall response rate or other secondary endpoints. Another Phase II study evaluated Sylvant in patients (n = 106) with previously untreated symptomatic multiple myeloma who were transplant-ineligible.[6] There was not a significant difference in complete response rate or overall response rate in patients treated with Velcade/melphalan/prednisone (VMP) vs. those treated with VMP + Sylvant. Progression-free survival and overall survival was the same in the two treatment groups. Another Phase II study in adults with relapsed or refractory multiple myeloma did not show any response with Sylvant monotherapy compared with 8% response rate in those who received Sylvant + dexamethasone.[7]

3. **Myelodysplastic Syndrome (MDS).** Efficacy is not established. A double-blind, placebo-controlled, Phase II study assigned adults with MDS (n = 76) to treatment with best supportive care in combination with Sylvant or placebo.[5] There was not a significant difference in the proportion of patients with reduced transfusions to treat anemia (primary endpoint). The study was terminated early due to lack of efficacy.

4. **Prostate Cancer.** Efficacy is not established. An open-label Phase II study did not demonstrate added efficacy with Sylvant added on to mitoxantrone/prednisone vs. mitoxantrone/prednisone.[8] Although the treatment groups were not balanced, progression-free survival was 97 days in the group that received Sylvant/mitoxantrone/prednisone vs. 228 days with mitoxantrone/prednisone. The study was stopped early.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

634. Sylvant® for intravenous injection [prescribing information]. Hemel Hempstead, Hertfordshire, UK: EUSA Pharma; February 2020.
635. Tanaka T, Kishimoto T. Targeting interleukin-6: all the way to treat autoimmune and inflammatory diseases. *Int J Biol Sci*. 2012;8(9):1227-1236.
636. The NCCN B-Cell Lymphoma Clinical Practice Guidelines in Oncology (version 1.2021 – January 20, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 26, 2021.
637. Orlowski RZ, Gercheva L, Williams C, et al. A phase 2, randomized, double-blind, placebo-controlled study of siltuximab (anti-IL-6 mAb) and bortezomib versus bortezomib alone in patients with relapsed or refractory multiple myeloma. *Am J Hematol*. 2015;90(1):42-49.
638. Garcia-Manero G, Gartenberg G, Steensma DP, et al. A phase 2, randomized, double-blind, multicenter study comparing siltuximab plus best supportive care (BSC) with placebo plus BSC in anemic patients with International Prognostic Scoring System low- or intermediate-1-risk myelodysplastic syndrome. *Am J Hematol*. 2014;89(9):E156-62.
639. San-Miguel J, Bladé J, Shpilberg O, et al. Phase 2 randomized study of bortezomib-melphalan-prednisone with or without siltuximab (anti-IL-6) in multiple myeloma. *Blood*. 2014;123(26):4136-4142.
640. Voorhees PM, Manges RF, Sonneveld P, et al. A phase 2 multicentre study of siltuximab, an anti-interleukin-6 monoclonal antibody, in patients with relapsed or refractory multiple myeloma. Br J Haematol. 2013;161(3):357-366.
641. Fizazi K, De Bono JS, Flechon A, et al. Randomised phase II study of siltuximab (CNTO 328), an anti-IL-6 monoclonal antibody, in combination with mitoxantrone/prednisone versus mitoxantrone/prednisone alone in metastatic castration-resistant prostate cancer. *Eur J Cancer*. 2012;48(1):85-93.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	02/20/2019
Annual Revision	No criteria changes.	02/19/2020
Selected Revision	**COVID-19:** This indication (including use for cytokine release syndrome associated with COVID-19) was added to the policy as a Condition Not Recommended for Coverage. All reviews are directed to the Medical Director.	03/27/2020
Annual Revision	No criteria changes.	02/17/2021

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Synribo Prior Authorization Policy

- Synribo® (omacetaxine mepesuccinate injection for subcutaneous use – Teva)

REVIEW DATE: 09/09/2020

OVERVIEW

Synribo is indicated for the treatment of chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKIs) in adults.[1] The safety and efficacy of Synribo in pediatric patients have not been established.

Disease Overview

CML is a myeloproliferative neoplasm that comprises 15% of newly-diagnosed adult leukemias with an incidence of 1 to 2 cases per 100,000 adults.[2,3] In 2020, it was estimated that 8,450 patients would be diagnosed in the US, and 1,130 patients would die from the disease.[2] The median age at onset is 67 years; however, CML occurs in all age groups. CML is diagnosed by persistent unexplained leukocytosis with the presence of the Philadelphia chromosome abnormality characterized by a reciprocal translocation between chromosomes 9 and 22 that gives rise to the breakpoint cluster region (*BCR*) Abelson murine leukemia (*ABL*) 1 fusion gene which is believed to play a central role in the initial development of CML. Approximately 50% of patients with CML that are diagnosed in the US are asymptomatic.[3] Diagnosis often occurs following a routine physical examination or blood test.[2,3] CML occurs in three different phases (chronic phase [CP], accelerated phase [AP], or blast phase [BP]) and is usually diagnosed in

CP. Common signs and symptoms of CP CML are related to anemia and splenomegaly. These include fatigue, weight loss, malaise, and left upper quadrant pain or fullness. Untreated CP CML will eventually progress to advanced disease in 3 to 5 years. Certain mutations are associated with high rates of disease progression and relapse. The T315I mutation is a commonly noted example, which occurs in about 5% to 15% of cases.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for CML (version 1.2021 – August 28, 2020) recommend Synribo as a treatment option for patients who have experienced disease progression to accelerated phase CML on TKI therapy.[2] It is not an option among patients who present with accelerated phase CML. Synribo is also a treatment option for patients with the T315I mutation. Synribo is stated as an option for patients with disease that is resistant and/or intolerant to two other TKIs.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Synribo. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Synribo as well as the monitoring required for adverse events and long-term efficacy, approval requires Synribo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Synribo is recommended in those who meet the following criteria:

FDA-Approved Indication

205. Chronic Myeloid Leukemia (CML). Approve for 6 months if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets one of the following criteria (i or ii):
  - **i.** Patient is T315I-positive; OR
  - **ii.** Patient has tried at least two tyrosine kinase inhibitors indicated for use in CML; AND
    Note: Examples include imatinib tablets, Sprycel® (dasatinib tablets), Tasigna® (nilotinib capsules), Bosulif® (bosutinib tablets), and Iclusig® (ponatinib tablets).
- **C)** Medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Synribo is not recommended in the following situations:

198. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

30. Synribo® injection for subcutaneous use [prescribing information]. North Wales, PS: Teva Pharmaceuticals; November 2019.
31. The NCCN Chronic Myeloid Leukemia Clinical Practice Guidelines in Oncology (Version 1.2021 – August 28, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 4, 2020.
32. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2020 update on diagnosis, therapy and monitoring. *Am J Hematol*. 2020;95(6):691-709.

HISTORY
Type of Revision	Summary of Changes	Review Date
New Policy	--	09/04/2019
Annual revision	For criteria related to chronic myeloid leukemia, examples of tyrosine kinase inhibitors used for this condition were removed from the criteria and placed in a Note.	09/09/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Tecartus Prior Authorization Policy
- Tecartus™ (brexucabtagene autoleucel suspension for intravenous injection – Kite Pharma)

REVIEW DATE: 08/05/2020

OVERVIEW
Tecartus, a CD19-directed genetically modified autologous T cell immunotherapy, is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma.[1] This indication was approved under accelerated approval based on the overall response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Tecartus is supplied in infusion bag(s) containing frozen suspension of genetically modified autologous T cells in human serum albumin.[1] Each bag is supplied in a metal cassette stored in the vapor phase of liquid nitrogen. Store Tecartus frozen in the vapor phase of liquid nitrogen and thaw prior to administration.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for B-cell lymphomas (version 3.2020 – August 4, 2020) recommend Tecartus for the subsequent treatment of relapsed or refractory mantle cell lymphoma, following treatment with chemoimmunotherapy and bruton tyrosine kinase inhibitor therapy.[2,3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tecartus. All approvals for therapy are provided for the approval duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Tecartus as well as the monitoring required for adverse events and long-term efficacy, approval requires Tecartus to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tecartus is recommended in those who meet the following criteria:

FDA-Approved Indications

206. Mantle Cell Lymphoma. Approve a single dose if the patient meets the following criteria (A, B, C, and D):

- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has previously received the following (i, ii, and iii):
  - **i.** Anthracycline- or bendamustine-based chemotherapy; AND
  - **ii.** An anti-CD20 monoclonal antibody; AND
  - **iii.** A Bruton tyrosine kinase inhibitor; AND
    Note: Bruton tyrosine kinase inhibitors include Brukinsa™ (zanubrutinib capsules), Calquence® (acalabrutinib capsules), and Imbruvica® (ibrutinib capules and tablets).
- **C)** Patient received lymphodepleting chemotherapy prior to Tecartus infusion; AND
- **D)** Tecartus is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tecartus is not recommended in the following situations:

199. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

642. Tecartus™ suspension for intravenous infusion [prescribing information]. Santa Monica, CA: Kite Pharma; July 2020.
643. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 3.2020 – August 4, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 5, 2020.
644. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 5, 2020. Search term: brexucabtagene.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/05/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Tecentriq Prior Authorization Policy
- Tecentriq® (atezolizumab injection for intravenous use – Genentech/Roche)

REVIEW DATE: 12/09/2020

OVERVIEW

Tecentriq, a programmed death-ligand 1 (PD-L1) blocking antibody, is indicated for the treatment of the following indications:[1]

- **Breast cancer**, in combination with paclitaxel protein-bound (Abraxane) for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells of any intensity covering ≥ 1% of the tumor area), as determined by an FDA-approved test. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
- **Hepatocellular carcinoma**, in combination with bevacizumab, for the treatment of patients with unresectable or metastatic hepatocellular carcinoma who have not received prior systemic therapy.
- **Melanoma**, in combination with Cotellic (cobimetinib tablets) and Zelboraf (vemurafenib tablets), for the treatment of patients with *BRAF V600* mutation-positive unresectable or metastatic disease.
- **Metastatic non-small cell lung cancer** (NSCLC):
  - As a single agent, for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 staining ≥ 50% of tumor cells or PD-L1 staining of tumor infiltrating immune cells covering ≥ 10% of the tumor area), with no anaplastic lymphoma kinase (*ALK*) or epidermal growth factor receptor (*EGFR*) genomic tumor aberrations; OR
  - In combination with bevacizumab, paclitaxel, and carboplatin for the first-line treatment of patients with metastatic non-squamous NSCLC with no *ALK* or *EGFR* genomic tumor aberrations; OR
  - In combination with paclitaxel protein-bound and carboplatin, for the first-line treatment of adults with non-squamous metastatic NSCLC with no *ALK* or *EGFR* genomic tumor aberrations; OR
  - As a single-agent, in patients who have disease progression during or following platinum-containing chemotherapy. Patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Tecentriq.
- **Small cell lung cancer**, in combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage SCLC.
- **Urothelial carcinoma**, in patients with locally advanced or metastatic disease who:
  - Are not eligible for cisplatin-based chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor infiltrating immune cells covering ≥ 5% of the tumor area); OR
  - Are not eligible for any platinum-containing chemotherapy regardless of the PD-L1 status; OR
  - Have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Tecentriq. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tecentriq as well as the monitoring required for adverse events and long-term efficacy, approval requires the medication to be prescribed by or in consultation with a prescriber who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Tecentriq is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Breast Cancer.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
   - **A)** Patient has unresectable locally advanced or metastatic triple-negative breast cancer; AND
     Note: Triple-negative breast cancer is estrogen receptor-negative, progesterone receptor-negative, and human epidermal growth factor 2 (HER2)-negative.
   - **B)** The tumor is programmed death-ligand 1 (PD-L1)-positive; AND
     Note: PD-L1 stained tumor infiltrating immune cells covering ≥ 1% of the tumor area.
   - **C)** The medication will be used in combination with Abraxane (paclitaxel albumin-bound for injection); AND
   - **D)** The medication is prescribed by or in consultation with an oncologist.

2. **Hepatocellular Carcinoma.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
   - **A)** Patient has unresectable or metastatic hepatocellular carcinoma; AND
   - **B)** Patient has not received prior systemic therapy; AND
   - **C)** The medication will be used in combination with bevacizumab; AND
   - **D)** The medication is prescribed by or in consultation with an oncologist.

3. **Melanoma.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   - **A)** Patient has unresectable or metastatic melanoma; AND
   - **B)** Patient has *BRAF V600* mutation-positive disease; AND
   - **C)** The medication will be used in combination with Cotellic (cobimetinib tablets) and Zelboraf (vemurafenib tablets); AND
   - **D)** The medication is prescribed by or in consultation with an oncologist.

4. **Non-Small Cell Lung Cancer.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **C)** Patient has advanced or metastatic disease; AND
   - **D)** Patient meets one of the following (i, ii, or iii):
     - ~~**A)**~~ Patient has non-squamous NSCLC (i.e., adenocarcinoma, large cell, or NSCLC not otherwise specified) and the patient meets the following criteria (a and b):
       - **a)** The tumor is negative for actionable mutations; AND

Note: Examples of actionable mutations include epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, *ROS1*, *BRAF V600E, MET exon 14* skipping mutation, *RET* rearrangement.

b) Patient meets one of the following [(1),(2), or (3)]:

(1) Patient's tumor expresses programmed death-ligand 1 (PD-L1) ≥ 50% as determined by an approved test; OR
Note: In this setting Tecentriq can be used either as a single agent or in combination with other agents.

(2) The medication will be used in combination with chemotherapy; OR
Note: Examples of chemotherapy regimens may include bevacizumab, paclitaxel, and carboplatin, carboplatin and Abraxane (paclitaxel, albumin-bound for injection).

(3) The medication is used as continuation maintenance therapy.
Note: Tecentriq can be used in combination with bevacizumab or as single agent in this setting.

ii. Patient has squamous cell NSCLC and meets both of the following (a and b):

a) The tumor is negative for actionable mutations; AND
Note: Examples of actionable mutations include epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, *ROS1*, *BRAF V600E, MET exon 14* skipping mutation, *RET* rearrangement.

b) Patient's tumor expresses programmed death-ligand 1 (PD-L1) ≥ 50% as determined by an approved test; OR

iii. The tumor is positive for actionable mutations and the patient has tried at least one of the targeted therapy options; AND
Note: Examples of actionable mutations include epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, *ROS1*, *BRAF V600E, MET exon 14* skipping mutation, *RET* rearrangement.

C) The medication is prescribed by or in consultation with an oncologist.

4. Small Cell Lung Cancer. Approve for 1 year if Tecentriq is prescribed by or in consultation with an oncologist.

5. Urothelial Carcinoma. Approve for 1 year if the patient meets the following criteria (A and B):

I) Patient meets ONE of the following conditions (i, ii, or iii):

i. According to the prescriber, the patient meets both of the following (a and b):

a) Patient is not eligible for cisplatin-based chemotherapy; AND

b) Patient's tumor expresses PD-L1 (i.e., PD-L1 stained tumor infiltrating immune cells covering ≥ 5% of the tumor area); OR

ii. According to the prescriber, the patient is not eligible for platinum-containing chemotherapy (i.e., cisplatin and carboplatin); OR
Note: This is regardless of the PD-L1 status.

iii. Patient has tried at least one platinum- (cisplatin or carboplatin) containing chemotherapy; AND

J) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tecentriq is not recommended in the following situations:

283. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

352. Tecentriq® injection for intravenous use [prescribing information]. South San Francisco, CA: Genentech, Inc (A member of the Roche Group); November 2020.
353. The NCCN Drugs & Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 2, 2020. Search term: atezolizumab.
354. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 1.2021 – November 25, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 7, 2020.
355. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (Version 6.2020 – July16, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 6, 2020.
356. The NCCN Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 1.2021 – August 11, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 6, 2020.
357. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 6.2020 – September 8, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: www.nccn.org. Accessed on December 7, 2020.
358. The NCCN Hepatobiliary Cancers Clinical Practice Guidelines in Oncology (Version 5.2020 – August 4, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 6, 2020.
359. The NCCN Melanoma: Cutaneous Clinical Practice Guidelines in Oncology (Version 1.2021 – November 25, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: www.nccn.org. Accessed on December 2, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	New criteria	11/13/2019
Selected Revisions	• **NSCLC:** Updated criteria for non-squamous cell carcinoma to include additional targetable mutations and PD-L1 expression of ≥ 50% and ≥ 1% to 49%. Added criteria for squamous cell NSCLC and for patients that are targetable mutation positive. • **Hepatocellular carcinoma:** Added new approval condition and criteria.	06/24/2020
Annual Revision	• **Breast Cancer:** Added two new Notes; one to define triple-negative disease and second Note defining PD-L1 positivity. • **Melanoma:** Added new condition and criteria based on FDA approval. • **Non-Small Cell Lung Cancer:** Instead of "targetable" changed it to "actionable". Under non-squamous NSCLC, added a Note under criteria for PD-L1 ≥ 50% to state that Tecentriq can be used as single agent or in combination in this setting. Deleted part of the criteria, tumor has PD-L1 expression ≥ 1% to 49%; but kept the criteria that the medication is used in combination with chemotherapy. Added new criteria that Tecentriq is used for continuation maintenance therapy. Under criteria where tumor is positive for targetable mutations, deleted duplicate criteria that Tecentriq is used as subsequent therapy. This is not needed since criteria requires use of a targeted therapy. • **Urothelial Carcinoma:** Changed "prescribing physician" to "prescriber".	12/09/2020

NSCLC – Non-small cell lung cancer; PD-L1 – Programmed death-ligand 1.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Thiotepa Products Prior Authorization Policy

- Thiotepa injection for intravenous, intracavitary, or intravesical use (Tepadina® – Adienne SA, generics)

REVIEW DATE: 10/28/2020

OVERVIEW

Thiotepa is an alkylating agent indicated for:

- **Beta-thalassemia**, to reduce the risk of graft rejection when used in conjunction with high-dose busulfan and cyclophosphamide as a preparative regimen for allogeneic hematopoietic progenitor (stem) cell transplantation for pediatric patients with class 3 disease.[1]
- **Bladder cancer**, for superficial papillary carcinoma of the urinary bladder.[1,2]
- **Breast adenocarcinoma**.[1]

- **Neoplastic diseases of various serosal cavities**, for controlling intracavitary effusions secondary to diffuse or localized disease.
- **Ovarian adenocarcinoma**.

Guidelines

The National Comprehensive Cancer Network (NCCN) **bladder cancer** guidelines (version 6.2020 – July 16, 2020) state that intravesical thiotepa does not appear to be effective. NCCN recommends gemcitabine and mitomycin for intravesical chemotherapy.[5]

The NCCN **breast cancer** guidelines (version 6.2020 – September 8, 2020) do not provide any recommendations on the use of thiotepa in the management of breast cancer.[3]

The NCCN **central nervous system** (CNS) cancers guidelines (version 3.2020 – September 11, 2020) recommend thiotepa, in combination with carmustine or busulfan and cyclophosphamide, with stem cell rescue for consolidation therapy of primary CNS lymphoma.[6] NCCN recommends intra-cerebrospinal fluid thiotepa for the treatment of leptomeningeal metastases.

The NCCN **ovarian cancer** guidelines (version 1.2020 – March 11, 2020) do not provide any recommendations on the use of thiotepa in the management of ovarian cancer.[4]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of thiotepa. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because of the specialized skills required for evaluation and diagnosis of patients treated with thiotepa as well as the monitoring required for adverse events and long-term efficacy, approval requires thiotepa to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of thiotepa is recommended in those who meet the following criteria:

FDA-Approved Indications

207. Beta-Thalassemia. Approve for 1 month if the patient meets the following criteria (A, B, C, D, and E):
- **A)** Patient is ≤ 18 years of age; AND
- **B)** Patient has class 3 beta-thalassemia; AND
- **C)** Thiotepa will be used prior to allogeneic hematopoietic stem cell transplantation; AND
- **D)** Thiotepa will be used in combination with high-dose busulfan and cyclophosphamide; AND
- **E)** The medication is prescribed by or in consultation with an oncologist.

208. Bladder Cancer. Approve for 1 month if the patient meets the following criteria (A and B):
- **A)** Patient has superficial papillary carcinoma of the urinary bladder; AND
- **B)** The medication is prescribed by or in consultation with an oncologist.

209. Breast Cancer. Approve for 6 months if thiotepa is prescribed by or in consultation with an oncologist.

210. Malignant Effusions. Approve for 6 months if the patient meets the following criteria (A and B):
- **A)** Patient has intracavitary effusions secondary to diffuse or localized neoplastic disease; AND
- **B)** The medication is prescribed by or in consultation with an oncologist.

211. Ovarian Cancer. Approve for 6 months if thiotepa is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

212. Leptomeningeal Metastases. Approve for 6 months if thiopeta is prescribed by or in consultation with an oncologist.

213. Primary Central Nervous System Lymphoma. Approve for 3 months if the patient meets if the patient meets the following criteria (A and B):

A) Thiotepa is used as a component of high-dose chemotherapy followed by hematopoietic stem cell transplantation; AND

B) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of thiotepa is not recommended in the following situations:

200. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

645. Tepadina® injection [prescribing information]. Lugano, Switzerland: Adienne SA; January 2017.
646. Thiotepa for injection [prescribing information]. Schaumberg, IL: Sagent Pharmaceuticals; April 2018.
647. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 6.2020 – September 8, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed October 12, 2020.
648. The NCCN Ovarian Cancer Clinical Practive Guidelines in Oncology (Version 1.2020 – March 11, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at; http://www.nccn.org. Accessed October 12, 2020.
649. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (Version 6.2020 – July 16, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 12, 2020.
650. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (Version 3.2020 – September 11, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 12, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/16/2019
Annual Revision	No criteria changes.	10/28/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Topotecan Products Prior Authorization Policy

- Hycamtin® (topotecan capsule – Novartis)
- Topotecan injection for intravenous use (Hycamtin® – Novartis, generics)

REVIEW DATE: 12/16/2020

OVERVIEW

Topotecan injection, a topoisomerase inhibitor, is indicated for the treatment of patients with:

- **Cervical cancer**, stage IV-B, recurrent, or persistent disease which is not amenable to curative treatment, in combination with cisplatin.
- **Metastatic ovarian cancer**, after disease progression on or after initial or subsequent chemotherapy, as a single agent.
- **Small cell lung cancer** (SCLC), platinum-sensitive disease who progressed at least 60 days after initiation of first-line chemotherapy, as a single agent.[1]

Guidelines

Topotecan is included in a variety of National Comprehensive Cancer Network (NCCN) guidelines:

- The NCCN **bone cancer** (Version 1.2021 – November 20, 2020) clinical practice guidelines recommend topotecan in combination with cyclophosphamide, as second-line therapy for patients with relapsed/refractory, or metastatic osteosarcoma and Ewing sarcoma (both category 2A), and dedifferentiated chondrosarcoma, high-grade undifferentiated pleomorphic sarcoma, and mesenchymal chondrosarcoma (category 2B).[2,7]
- The NCCN **central nervous system** cancers (Version 3.2020 – September 11, 2020) clinical practice guidelines recommend topotecan as a single agent for the treatment of brain metastases in patients with small cell lung cancer.[2,8] In addition, the guidelines recommend intra-cerebrospinal fluid topotecan for the treatment of leptomeningeal metastases.
- The NCCN **cervical cancer** (Version 1.2021 – October 2, 2020) clinical practice guidelines recommend topotecan as first- or second-line therapy for patients with local/regional recurrence, stage IV-B disease, or distant metastases and as second-line therapy for patients with persistent, recurrent, or metastatic small cell neuroendocrine carcinoma of the cervix.[2,5] Topotecan can be used in combination with paclitaxel with or without bevacizumab, in combination with cisplatin, or as a single agent for second-line therapy (category 2B recommendation).
- The NCCN **Merkel cell carcinoma** (Version 1.2020 – October 2, 2019) clinical practice guidelines recommend topotecan as a treatment option for patients with distant metastatic disease who have contraindications to checkpoint immunotherapy (Bavencio® [avelumab injection for intravenous use], Keytruda® [injection for intravenous use], and Opdivo® [injection for intravenous use].[2,9]
- The NCCN **ovarian cancer** (Version 1.2020 – March 11, 2020) clinical practice guidelines recommend topotecan, as a single agent or in combination with bevacizumab or Nexavar® (sorafenib tablet), for the treatment of recurrent or persistent platinum-resistant epithelial ovarian cancer, fallopian tube cancer, and peritoneal cancer.[2,3] Treatment of clinical relapse is a category 2A recommendation and immediate treatment of biochemical relapse is category 2B recommendation.
- The NCCN **soft tissue sarcoma** (Version 1.2021 – October 30, 2020) clinical practice guidelines recommend topotecan as a single agent or in combination with cyclophosphamide for the treatment of non-pleomorphic rhabdomyosarcoma.[2,10]
- The NCCN **SCLC** (Version 1.2021 – August 11, 2020) clinical practice guidelines recommend topotecan as a single agent for patients with a performance status of 0-2 and relapse within 6 months following complete or partial response, or stable disease with initial treatment; or for primary progressive disease.[2,4]
- The NCCN **uterine cancer** (Version 1.2021 – October 20, 2020) clinical practice guidelines recommend topotecan as a single agent for the treatment of recurrent, metastatic, or high-risk endometrial carcinoma.[2,6]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of topotecan. All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with topotecan as well as the monitoring required for adverse events and long-term efficacy, approval requires topotecan to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of topotecan is recommended in those who meet the following criteria:

FDA-Approved Indications

214. Cervical Cancer. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient meets one of the following (i or ii):
  - **i.** Patient has persistent or recurrent disease; OR
  - **ii.** Patient has metastatic disease; AND
- **B)** Topotecan is prescribed by or in consultation with an oncologist.

215. Ovarian, Fallopian Tube, and Primary Peritoneal Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient has persistent or recurrent disease; AND
- **B)** The cancer is platinum-resistant; AND
- **C)** Topotecan is prescribed by or in consultation with an oncologist.

216. Small Cell Lung Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient meets one of the following (i or ii):
  - **i.** Patient has relapsed disease; OR
  - **ii.** Patient has primary progressive disease; AND
- **B)** Topotecan will be used as a single agent; AND
- **C)** Topotecan is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

217. Bone Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
- **A)** Patient has one of the following (i, ii, iii, iv, or v):
  - **i.** Osteosarcoma; OR
  - **ii.** Ewing sarcoma; OR
  - **iii.** Dedifferentiated chondrosarcoma; OR
  - **iv.** High-grade undifferentiated pleomorphic sarcoma; OR
  - **v.** Mesenchymal chondrosarcoma; AND
- **B)** Patient has relapsed, refractory, or metastatic disease; AND
- **C)** Topotecan is used second-line; AND
- **D)** Topotecan is used in combination with cyclophosphamide; AND
- **E)** Topotecan is prescribed by or in consultation with an oncologist.

218. Brain Metastases. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient has small cell lung cancer; AND
- **B)** Topotecan will be used as a single agent; AND
- **C)** Topotecan is prescribed by or in consultation with an oncologist.

219. Endometrial Carcinoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient has recurrent, metastatic, or high-risk disease; AND
- **B)** Topotecan will be used as a single agent; AND
- **C)** Topotecan is prescribed by or in consultation with an oncologist.

220. Leptomeningeal and Spinal Metastases. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Topotecan will be administered intraventricularly; AND
- **B)** Topotecan is prescribed by or in consultation with an oncologist.

221. Merkel Cell Carcinoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient has distant metastatic disease; AND
- **B)** Patient has contraindications to checkpoint immunotherapy; AND
  Note: Checkpoint immunotherapy includes Bavencio® (avelumab injection for intravenous use), Keytruda® (injection for intravenous use), and Opdivo® (injection for intravenous use).
- **C)** Topotecan is prescribed by or in consultation with an oncologist.

222. Rhabdomyosarcoma. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Patient has non-pleomorphic rhabdomyosarcoma; AND
- **B)** Topotecan is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of topotecan is not recommended in the following situations:

201. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

651. Hycamtin injection for intravenous use [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals; October 2019.
652. The NCCN Drugs & Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 10, 2020. Search term: topotecan.
653. The NCCN Ovarian Cancer Clinical Practice Guidelines (Version 1.2020 – March 11, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 10, 2020.
654. The NCCN Small Cell Lung Cancer Clinical Practice Guidelines (Version 1.2021 – August 11, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 11, 2020.
655. The NCCN Cervical Cancer Clinical Practice Guidelines (Version 1.2021 – October 2, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 10, 2020.
656. The NCCN Uterine Cancer Clinical Practice Guidelines (Version 1.2021 – October 20, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 11, 2020.
657. The NCCN Bone Cancer Clinical Practice Guidelines (Version 1.2021 – November 20, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 11, 2020.
658. The NCCN Central Nervous System Cancers Clinical Practice Guidelines (Version 3.2020 – September 11, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 10, 2020.
659. The NCCN Merkel Cell Carcinoma Clinical Practice Guidelines (Version 1.2020 – October 2, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 25, 2019.
660. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines (Version 1.2021 – October 30, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 11, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/18/2009
Annual Revision	**Cervical cancer**. Revised criteria from patient has local/regional recurrence to patient has persistent or recurrent disease. Removed distant from patient has distant metastases. **Brain metastases**. Removed the patient has recurrent disease criteria. **Primary central nervous system lymphoma**. Remove criteria from the policy (use is no longer supported in guidelines).	12/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Torisel Prior Authorization Policy

- Torisel® (temsirolimus injection for intravenous use – Wyeth Pharmaceuticals)

REVIEW DATE: 10/28/2020

OVERVIEW

Torisel, an inhibitor of mammalian target of rapamycin (mTOR), is indicated for the treatment of **advanced renal cell carcinoma**.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for **kidney cancer** (version 1.2021 – July 15, 2020) recommend Torisel as a single agent for the treatment of relapsed or stage IV renal cell carcinoma.[2,3]

The NCCN guidelines for **soft tissue sarcoma** (version 2.2020 – May 28, 2020) recommend Torisel as a single agent for the treatment of perivascular epithelioid cell tumors (PEComas), and lymphangioleiomyomatosis or angiomyolipomas.[2,4]

The NCCN guidelines for **uterine neoplasms** (version 2.2020 – July 24, 2020) recommend Torisel as a single-agent for the treatment of recurrent, metastatic, or high-risk endometrial cancer.[2,5]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Torisel. All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Torisel as well as the monitoring required for adverse events and long-term efficacy, approval requires Torisel to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Torisel is recommended in those who meet the following criteria:

FDA-Approved Indications

223. Renal Cell Carcinoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):

A) Patient has relapsed, advanced, or metastatic disease; AND

B) Torisel will be used as a single-agent; AND

C) The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

224. Endometrial Carcinoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient has recurrent, metastatic, or high-risk disease; AND
- **B)** Torisel will be used as a single-agent; AND
- **C)** The medication is prescribed by or in consultation with an oncologist.

225. Soft Tissue Sarcoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient has one of the following (i, ii, or iii):
  - **i.** Perivascular epithelioid cell tumors (PEComas); OR
  - **ii.** Lymphangioleiomyomatosis; OR
  - **iii.** Recurrent angiomyolipoma; AND
- **B)** Torisel will be used as a single-agent; AND
- **C)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Torisel is not recommended in the following situations:

202. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

661. Torisel® injection for intravenous use [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals; March 2018.
662. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 13, 2020.
663. The NCCN Kidney Cancer Clinical Practice Guidelines in Oncology (Version 1.2021 – July 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 13, 2020.
664. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (Version 2.2020 – May 28, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 13, 2020.
665. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (Version 2.2020 – July 24, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 13, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/16/2019
Annual Revision	No criteria changes.	10/28/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Trastuzumab Products
- Herceptin® (trastuzumab intravenous infusion – Genentech, Inc.)
- Herzuma® (trastuzumab-pkrb injection for intravenous infusion – Celltrion)
- Ogivri™ (trastuzumab-dkst injection for intravenous infusion – Mylan)
- Ontruzant® (trastuzumab-dttb injection for intravenous infusion – Merck)
- Trazimera™ (trastuzumab-qyyp injection for intravenous infusion – Pfizer)
- Kanjinti™ (trastuzumab-anns injection for intravenous infusion – Amgen)

DATE REVIEWED: 06/10/2020

OVERVIEW

Herceptin is indicated for adjuvant treatment of human epidermal growth factor receptor 2 (HER2) overexpressing node positive or node negative (estrogen receptor [ER]/progesterone receptor [PR] negative or with one high risk feature) breast cancer 1) as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel; 2) with docetaxel and carboplatin; or 3) as a single agent following multi-modality anthracycline based therapy.[1] Herceptin is also indicated for the treatment of HER2 overexpressing metastatic breast cancer, either in combination with paclitaxel for first-line treatment, or as a single agent in patients who have received one or more chemotherapy regimens. In addition, Herceptin is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil (5-FU), for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal (GE) junction adenocarcinoma, who have not received prior treatment for metastatic disease. For all indications, patients must be selected for therapy based on an FDA-approved companion diagnostic for Herceptin. Tests are specific for breast cancer or gastric cancer.

Guidelines

The National Comprehensive Cancer Network (NCCN) breast cancer guidelines (version 4.2020 – May 8, 2020) recommend trastuzumab in combination with chemotherapy and endocrine therapy for adjuvant treatment of HER2-positive breast cancer (category 1).[2] Perjeta® (pertuzumab intravenous injection) can also be added to this treatment regimen (category 2A). The preferred first-line agents for HER2-positive *recurrent or metastatic disease* (either hormone receptor-negative or hormone receptor-positive and refractory to endocrine therapy) include: Perjeta plus trastuzumab plus docetaxel (category 1) or paclitaxel (category 2A). The guidelines list other trastuzumab-containing regimens for HER2-positive metastatic disease.

The NCCN clinical practice guidelines on gastric cancer (version 2.2020 – May 13, 2020) and on esophageal and esophagogastric junction cancers (version 2.2020 – May 13, 2020) state that for metastatic or locally advanced disease (where local therapy is not indicated) trastuzumab should be added to first-line systemic chemotherapy for HER2-overexpressing adenocarcinoma.[3,4] The recommended regimens for metastatic or locally advanced HER2-positive gastric, esophageal, or esophagogastric junction adenocarcinoma are trastuzumab in combination with cisplatin and a fluoropyrimidine (5-FU or capecitabine) [category 1] or trastuzumab in combination with other chemotherapy agents (category 2B) [various regimens based on individual patient variability]. Trastuzumab is not recommended for use in combination with anthracyclines.

Uterine serous carcinoma is a rare, aggressive histology of endometrial cancer. The NCCN guidelines for uterine neoplasms (version 1.2020 – March 6, 2020) lists the combination chemotherapy regimen of carboplatin/paclitaxel/trastuzumab as one of the recommended therapies for patients with HER2-positive uterine serous carcinoma (category 2A).[6]

The NCCN Compendium recommends use of trastuzumab for endometrial carcinoma and rectal or colon cancer.[5]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of trastuzumab products. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with trastuzumab products, as well as the monitoring required for adverse events

and long-term efficacy, approval requires trastuzumab products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of trastuzumab products is recommended in those who meet the following criteria:

FDA-Approved Indications

30. Breast Cancer. Approve if the patient meets the following criteria (A, B, and C):
- **A)** The medication is prescribed by or in consultation with an oncologist; AND
- **B)** The patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
- **C)** The patient meets ONE of the following criteria (i or ii):

  i. Approve for 1 year (total) if trastuzumab is used for neoadjuvant (preoperative)/adjuvant therapy; OR

  ii. Approve for 1 year if trastuzumab is used for recurrent or metastatic disease.

31. Gastric, Esophageal, or Gastroesophageal Junction Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** The medication is prescribed by or in consultation with an oncologist; AND
- **B)** The patient has human epidermal growth factor receptor 2 (HER2)-positive locally advanced or metastatic disease; AND
- **C)** Trastuzumab will be used first-line in combination with chemotherapy.
  Note: Examples of chemotherapy are cisplatin, oxaliplatin, capecitabine, 5-fluorouracil (5-FU).

Other Uses with Supportive Evidence

3. Endometrial Carcinoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** The medication is prescribed by or in consultation with an oncologist; AND
- **B)** The patient has human epidermal growth factor receptor 2 (HER2)-positive advanced or recurrent uterine serous carcinoma; AND
- **C)** Trastuzumab will be used in combination with chemotherapy.
  Note: Examples of chemotherapy are carboplatin, paclitaxel.

4. Colon or Rectal Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** The medication is prescribed by or in consultation with an oncologist; AND
- B) The patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
- **C)** The medication is used in combination with Perjeta® (pertuzumab for injection) or Tykerb® (lapatinib tablets).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Trastuzumab has not been shown to be effective or there are limited or preliminary data that are not supportive of general approval for the following conditions.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

17. Herceptin® for injection for intravenous use [prescribing information]. South San Francisco, CA: Genentech, Inc.; November 2018.
18. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 4.2020 – May 8, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 7, 2020.
19. The NCCN Gastric Clinical Practice Guidelines in Oncology (Version 2.2020 – May 13, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 7, 2020.
20. The NCCN Esophageal and Esophagogastric Junction Cancers Clinical Practice Guidelines in Oncology (Version 2.2020 – May 13, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 7, 2020.
21. The NCCN Drugs & Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 7, 2020. Search term: trastuzumab.

HISTORY

Type of Revision	Summary of Changes*	Date Reviewed
Annual revision	No criteria changes.	04/06/2016
Annual revision	No criteria changes.	05/24/2017
Annual revision	No criteria changes.	06/27/2018
Annual revision	Changed name of policy to Trastuzumab Products due to the approval of several biosimilars. Changed intent of the policy from a pharmacogenomics PA to a regular PA policy. **Breast Cancer.** Added new criteria to ask for prescriber specialty, HER2-positive disease, and to approve for 1 year (total) for neoadjuvant/adjuvant therapy and approve 1 year for metastatic disease. **Gastric, Esophageal, or Gastroesophageal (GE) Junction Cancer.** Added "Esophageal" to the condition approval. Specified that trastuzumab will be used "first-line" in combination with "chemotherapy" and the examples are listed as a Note. Added requirement for prescriber specialty and HER2-positive disease. **Endometrial Carcinoma.** Added new approval condition under "Other Uses with Supportive Evidence" based on guidelines/compendium support.	07/31/2019
Early annual revision	Added new condition of approval for Colon or Rectal Cancer based on guidelines.	06/10/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Trodelvy™ (sacituzumab govitecan-hziy injection for intravenous use – Immunomedics, Inc.)

DATE REVIEWED: 04/23/2020

OVERVIEW

Trodelvy, a Trop-2-directed antibody and topoisomerase inhibitor conjugate, is indicated for the treatment of adult patients with metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease.[1] This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication maybe contingent upon verification and description of clinical benefit in trials.

Guidelines

Trodelvy is not addressed in the guidelines. According to the National Comprehensive Cancer Network (NCCN) breast cancer guidelines (version 3.2020 – March 6, 2020), systemic therapy options for metastatic disease include a variety of chemotherapy agents such as carboplatin or cisplatin (specified for TNBC and germline BRCA 1/2 mutation), Tecentriq (atezolizumab for injection) + Abraxane (albumin-bound paclitaxel for injection) [for programmed death ligand-1 {PD-L1} expression ≥ 1%], paclitaxel,

cyclophosphamide, doxorubicin, Doxil (liposomal doxorubicin for injection), capecitabine, gemcitabine, docetaxel, epirubicin, vinorelbine, eribulin.[2] Single agents are preferred; however, chemotherapy combinations may be used in patients with high tumor burden, rapidly progressing disease, and visceral crisis.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Trodelvy. All approvals are provided for the duration noted below. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Trodelvy, as well as the monitoring required for adverse events and long-term efficacy, approval requires Trodelvy to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Trodelvy is recommended in those who meet the following criteria:

FDA-Approved Indications

32. Breast Cancer. Approve for 1 year if the patient meets ALL of the criteria (A, B, C, and D):

A) The patient is ≥ 18 years of age; AND

B) The patient has metastatic triple-negative breast cancer; AND

C) The patient has been previously treated with at least two systemic therapy regimens for metastatic disease.

Note: Examples are cisplatin, carboplatin, doxorubicin, cyclophosphamide, paclitaxel, docetaxel, capecitabine, gemcitabine, ixabepilone, vinorelbine, eribulin, epirubicin, Doxil (liposomal doxorubicin for injection), Tecentriq (atezolizumab for injection) + Abraxane (albumin-bound paclitaxel for injection); AND

D) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Trodelvy has not been shown to be effective or there are limited or preliminary data that are not supportive of general approval for the following conditions.

7. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

22. Trodelvy™ injection for intravenous use [prescribing information]. Morris Plains, NJ: Immunomedics, Inc.; April 2020.
23. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 3.2020 – March 6, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on April 22, 2020.

HISTORY

Type of Revision	Summary of Changes*	Date Reviewed
New policy	New criteria	04/23/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Unituxin Prior Authorization Policy

- Unituxin® (dinutuximab injection for intravenous use – United Therapeutics Corp)

REVIEW DATE: 12/02/2020

OVERVIEW

Unituxin, a glycolipid disialoganglioside (GD2)-binding monoclonal antibody, is indicated for the treatment of pediatric patients with high-risk **neuroblastoma** who achieve at least a partial response to prior first-line multi-agent, multimodality therapy, in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-cis-retinoic acid.[1]

Guidelines

Unituxin is not addressed in National Comprehensive Cancer Network treatment guidelines.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Unituxin. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Unituxin as well as the monitoring required for adverse events and long-term efficacy, approval requires Unituxin to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Unituxin is recommended in those who meet the following criteria:

FDA-Approved Indications

226. Neuroblastoma. Approve for 6 months if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≤ 18 years of age; AND
- **B)** Unituxin is used as subsequent therapy; AND
- **C)** Unituxin is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Unituxin is not recommended in the following situations:

203. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

666. Unituxin injection for intravenous use [prescribing information]. Silver Spring, ND: United Therapeutics Corp.; March 2017.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/02/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Vectibix Prior Authorization Policy

- Vectibix® (panitumumab solution for intravenous infusion – Amgen Inc.)

REVIEW DATE: 07/22/2020

OVERVIEW

Vectibix, an epidermal growth factor receptor monoclonal antibody, is indicated for the treatment of wild-type *RAS* (defined as wild-type in both KRAS and NRAS as determined by an FDA-approved test for this use) metastatic colorectal cancer (mCRC) as a) first-line therapy in combination with FOLFOX (5-fluorouracil [5-FU], leucovorin, oxaliplatin) or b) monotherapy following disease progression after prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy.[1] It is a limitation

of use that Vectibix is not indicated for the treatment of patients with *RAS*-mutant mCRC or for whom *RAS* mutation status is unknown.

Guidelines

Colon Cancer

The National Comprehensive Cancer Network (NCCN) colon cancer guidelines (version 4.2020 – June 15, 2020) recommend Vectibix as primary therapy for unresectable, advanced, or metastatic *KRAS/NRAS/BRAF* wild-type gene and left-sided tumors only in combination with irinotecan, FOLFOX, FOLFIRI (5-FU, leucovorin, irinotecan), or FOLFOXIRI (5-FU, leucovorin, oxaliplatin, irinotecan) regimens in patients who can tolerate intensive therapy or as a single agent in patients who cannot tolerate intensive therapy.[2,4] Reference to left-sided only disease refers to a primary tumor that originated in the left side of the colon and only refers to use of Vectibix as first-line therapy for metastatic disease. Therapies recommended after first progression vary depending on the initial treatment regimen (i.e., 5-FU/leucovorin-based or capecitabine-based therapy) that was used. The NCCN guidelines recommend Vectibix, in combination with irinotecan, FOLFOX, or FOLFIRI for the subsequent treatment of *KRAS/NRAS/BRAF* wild-type tumors; or in combination with Braftovi (encorafenib capsules) for the subsequent treatment of *BRAF V600E* positive disease. The NCCN rectal cancer guidelines (version 6.2020 – June 25, 2020) make the same recommendations for Vectibix for the treatment of rectal cancer.[3,4]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Vectibix. All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Vectibix as well as the monitoring required for adverse events and long-term efficacy, approval requires Vectibix to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vectibix is recommended in those who meet the following criteria:

FDA-Approved Indications

27. Colon and Rectal Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
- **A)** Patient has advanced or metastatic disease; AND
- **B)** Patient's tumor or metastases are wild-type *RAS* (*KRAS* wild-type and/or *NRAS* wild-type) [that is, the tumor or metastases are *KRAS* and/or *NRAS* mutation negative]; AND
- **C)** If Vectibix is being used for first-line treatment, the primary tumor originated on the left side of the colon (from splenic flexure to rectum); AND
- **D)** Patient meets ONE of the following criteria (i or ii):
  - **i.** Patient's tumor or metastases are wild-type *BRAF* (that is, the tumor or metastases are *BRAF V600E* mutation negative); OR
  - **ii.** Patient's tumor or metastases are *BRAF V600E* mutation-positive and the patient meets the following (a and b):
    - **a)** Patient has previously received a chemotherapy regimen for colon or rectal cancer; AND
      Note: Examples of chemotherapy regimens include a fluoropyrimidine such as 5-fluorouracil (5-FU), capecitabine, oxaliplatin, irinotecan, or an adjunctive chemotherapy

regimen such as FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).

b) Vectibix is prescribed in combination with Braftovi (encorafenib capsules).

E) Vectibix is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vectibix is not recommended in the following situations:

204. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

33. Vectibix® injection for intravenous infusion [prescribing information]. Thousand Oaks, CA: Amgen Inc; June 2017.
34. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 4.2020 – June 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 16, 2020.
35. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (Version 6.2020 – June 25, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 16, 2020.
4. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 15, 2020. Search term: panitumumab.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/24/2019
Annual revision	Revised *BRAF V600E* mutation-positive disease combination therapy criteria to only include Vectibix in combination with Braftovi (encorafenib capsules).	07/22/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Vyxeos Prior Authorization Policy

- Vyxeos® (daunorubicin and cytarabine liposome for injection – Jazz Pharmaceuticals)

REVIEW DATE: 10/28/2020

OVERVIEW

Vyxeos is a liposomal combination of daunorubicin, an anthracycline topoisomerase inhibitor, and cytarabine, a nucleoside metabolic inhibitor, is indicated for the treatment of newly-diagnosed therapy-related **acute myeloid leukemia** (AML) or **AML with myelodysplasia-related changes** in adults.[1]

Guidelines

The National Comprehensive Cancer Network guidelines for **acute myeloid leukemia** (version 4.2020 – September 28, 2020) recommend Vyxeos for induction and post-remission therapy for patients with therapy-related AML, antecedent myelodysplastic syndrome/chronic myelomonocytic leukemia, and AML with myelodysplasia-related changes.[2,3]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Vyxeos. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Vyxeos as well as the monitoring required for adverse events and long-term efficacy, approval requires Vyxeos to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vyxeos is recommended in those who meet the following criteria:

FDA-Approved Indications

227. Acute Myeloid Leukemia. Approve for 6 months if the patient meets the following criteria (A, B, and C):

A) Patient is ≥ 18 years of age; AND

B) Patient meets one of the following (i or ii):

i. Patient has therapy-related acute myeloid leukemia; OR

ii. Patient has secondary acute myeloid leukemia; AND

Note: Examples include antecedent myelodysplastic syndrome/chronic myelomonocytic leukemia and acute myeloid leukemia with myelodysplasia-related changes.

C) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vyxeos is not recommended in the following situations:

205. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

667. Vyxeos liposome for injection [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals; July 2019.
668. The NCCN Drugs & Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 13, 2020. Search term: Vyxeos.
669. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (Version 4.2020 – September 28, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 13, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/16/2019
Annual Revision	No criteria changes.	10/28/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Yervoy Prior Authorization Policy

- Yervoy® (ipilimumab injection for intravenous use – Bristol-Myers Squibb)

REVIEW DATE: 10/07/2020

OVERVIEW

Yervoy, a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody, is indicated for the following conditions:

- **Melanoma**, unresectable or metastatic in adults and pediatric patients (≥ 12 years).
- **Melanoma**, for adjuvant treatment of cutaneous disease in patients with pathologic involvement of regional lymph nodes of > 1 mm who have undergone complete resection, including total lymphadenectomy.
- **Renal cell carcinoma (RCC)**, advanced, in combination with Opdivo® (nivolumab for intravenous injection) for the treatment of patients with intermediate or poor risk, previously untreated disease.
- **Colorectal cancer, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)**, in combination with Opdivo for the treatment of adult and pediatric patients ≥ 12 years of age with metastatic disease that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.[1]
- **Hepatocellular carcinoma**, in combination with Opdivo, for the treatment of patients who have been previously treated with Nexavar® (sorafenib tablets). This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
- **Malignant pleural mesothelioma**, in combination with Opdivo, for the first-line treatment of adult patients with unresectable disease.
- **Non-small cell lung cancer (NSCLC)**, in combination with Opdivo, for the first-line treatment of adult patients with metastatic disease whose tumors express programmed death ligand-1 (PD-L1) [≥ 1%], as determined by an FDA-approved test, with no epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations.
- **Non-small cell lung cancer (NSCLC)**, in combination with Opdivo and two cycles of platinum-doublet chemotherapy, for the first-line treatment of adult patients with metastatic or recurrent NSCLC, with no *EGFR* or *ALK* genomic tumor aberrations.

Guidelines

The National Comprehensive Cancer Network (NCCN) Compendium recommends Yervoy for the following indications: melanoma (uveal, cutaneous, and brain metastases), small bowel adenocarcinoma, kidney cancer, small cell lung cancer, malignant pleural mesothelioma, colon and rectal cancer, hepatocellular carcinoma, and non-small cell lung cancer (NSCLC).[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Yervoy. Because of the specialized skills required for evaluation and diagnosis of patients treated with Yervoy as well as the monitoring required for adverse events and long-term efficacy, approval requires the medication to be prescribed by or in consultation with a prescriber who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Yervoy is recommended in those who meet the following criteria:

FDA-Approved Indications

25. Colon or Rectal Cancer, Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR). Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
- **A)** Patient is ≥ 12 years of age; AND
- **B)** Patient meets ONE of the following criteria (i or ii):
  - **i.** Patient has tried chemotherapy; OR
    Note: Examples of chemotherapy are fluoropyrimidine such as 5-fluorouracil [5-FU], capecitabine~~,~~ oxaliplatin, irinotecan, or an adjunctive chemotherapy regimen such as FOLFOX [5-FU, leucovorin, and oxaliplatin] or CapeOX [capecitabine and oxaliplatin]).
  - **ii.** Patient has unresectable or metastatic disease and is not a candidate for intensive therapy, according to the prescriber; AND
- **C)** The medication will be used in combination with Opdivo (nivolumab intravenous injection); AND
- **D)** The medication is prescribed by or in consultation with an oncologist.

26. Hepatocellular Carcinoma. Approve for 4 months if the patient meets ALL of the following (A, B, and C):
- **A)** The medication is used in combination with Opdivo (nivolumab for injection); AND
- **B)** Patient has tried at least one tyrosine kinase inhibitor (TKI); AND
  Note: Examples are Nexavar (sorafenib tablets), Lenvima (levatinib capsules).
- **C)** The medication is prescribed by or in consultation with an oncologist.

27. Melanoma [Note: This includes cutaneous melanoma, brain metastases due to melanoma, and uveal melanoma]. Approve if the patient meets ALL of the following (A, B, and C):
- **A)** Patient is ≥ 12 years of age; AND
- **B)** Patient meets ONE of the following (i or ii):
  - **i.** Approve for 4 months if the patient has unresectable or metastatic melanoma; OR
  - **ii.** Approve for 1 year if Yervoy will be used as adjuvant treatment; AND
    Note: For example, in patients with cutaneous melanoma who have undergone complete resection, including total lymphadenectomy.
- **C**) The medication is prescribed by or in consultation with an oncologist.

28. Malignant Pleural Mesothelioma. Approve for 1 year if the patient meets the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has unresectable disease; AND
- **C)** The medication will be used in combination with Opdivo (nivolumab for intravenous injection); AND
- **D)** The medication is prescribed by or in consultation with an oncologist.

29. Non-Small Cell Lung Cancer (NSCLC). Approve for 1 year if the patient meets ALL of the following (A, B, C, D, E, and F):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has metastatic disease; AND
- **C)** Patient's tumor is negative for a targetable mutation; AND
  Note: Examples of targetable mutations include sensitizing epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, *ROS1*, *BRAF*, *MET 14* skipping mutation, *RET* rearrangement.
- **D)** The medication is used in combination with Opdivo (nivolumab for injection); AND
- **E)** Patient meets one of the following criteria (i or ii):
  - **i.** Patient's tumor expresses programmed death-ligand 1 (PD-L1) ≥ 1% as determined by an approved test; OR
  - **ii.** The medication is used in combination with platinum-doublet chemotherapy; AND

Note: Examples of platinum-doublet chemotherapies are carboplatin and Alimta (pemetrexed for injection), cisplatin and Alimta, carboplatin and paclitaxel.

F) The medication is prescribed by or in consultation with an oncologist.

30. Renal Cell Carcinoma. Approve for 4 months if the patient meets the following criteria (A, B, and C):

K) Patient has advanced (e.g., relapsed, Stage IV, metastatic) disease; AND

L) The medication will be used in combination with Opdivo (nivolumab for intravenous injection); AND

C) The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

7. Small Bowel Adenocarcinoma. Approve for 1 year if the patient meets the following (A, B, C, and D):

A) Patient has advanced or metastatic disease; AND

B) The tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND

C) The medication will be used in combination with Opdivo (nivolumab for intravenous injection); AND

D) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Yervoy is not recommended in the following situations:

284. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

446. Yervoy® Intravenous Infusion [prescribing information]. Bridgewater, NJ: Sanofi-Aventis; October 2020.

447. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 29, 2020. Search term: ipilimumab.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	New criteria	09/25/2019
Annual Revision	• **Hepatocellular Carcinoma:** Added new FDA-approved indication. • **Malignant Pleural Mesothelioma:** Moved from "Other Uses with Supportive Evidence" to FDA-approved use. Deleted criteria requiring prior therapy since it's approved for first-line use in adults. Added age criteria. • **Non-Small Cell Lung Cancer:** Added new FDA-approved indication. • **Small Bowel Adenocarcinoma:** Moved "Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR)" from indication to list it as criteria. • **Small Cell Lung Cancer:** Deleted approval condition since this indication is no longer supported in compendium/guidelines.	10/07/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Yescarta® (axicabtagene ciloleucel suspension for intravenous infusion – Kite Pharma)

DATE REVIEWED: 04/29/2020

OVERVIEW

Yescarta, a CD19-directed genetically modified autologous T cell immunotherapy, is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse B-cell lymphoma (DLBCL) not otherwise specified, primarily mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.[1] Yescarta has a Boxed Warning regarding cytokine release syndrome (CRS) and neurological toxicities. Due to these risks, Yescarta is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called Yescarta REMS.[1]

Yescarta is supplied as an infusion bag containing approximately 68 mL of frozen suspension of genetically modified autologous T cells in 5% DMSO and 2.5% albumin (human).[1] Yescarta is stored in the vapor phase of liquid nitrogen (less than or equal to minus 150°C) and supplied in a liquid nitrogen dry shipper.

Clinical Efficacy

The efficacy of Yescarta was established in one single-arm, open-label, Phase II, multicenter trial that included adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma (NHL) [ZUMA-1].[1-2] Yescarta was given as a single infusion after lymphodepleting chemotherapy. In total, 101 of 111 patients who underwent leukapheresis received Yescarta and most (76%) had DLBCL, 16% of patients had transformed follicular lymphoma, and 8% of patients had primary mediastinal large B-cell lymphoma. The median number of prior therapies was three. The median dose was 2.0×10^6 CAR-positive viable T cells.[1-2]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for B-cell lymphoma (version 1.2020 – January 22, 2020) recommend Yescarta for the treatment of a variety of B-cell lymphomas in patients with relapsed or refractory disease and after at least two chemotherapy regimens.[3,4] Recommended indications include DLBCL which transformed from follicular lymphoma or nodal marginal zone lymphoma, DLBCL, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, AIDS-related B-cell lymphoma, human herpes virus 8 (HHV8)-positive DLBCL, and post-transplant lymphoproliferative disorders (category 2A).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Yescarta. All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Yescarta as well as the monitoring required for adverse events and long-term efficacy, approval requires Yescarta to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Yescarta is recommended in those who meet the following criteria:

FDA-Approved Indications

28. B-Cell Lymphoma. Approve a single dose if the patient meets the following criteria (A, B, C, D, E, and F):

C) The patient meets one of the following diagnoses (i, ii, iii, iv, v, vi, vii, viii, or ix):

i. Large B-cell lymphoma; OR
ii. Diffuse large B-cell lymphoma; OR
iii. Primary mediastinal large B-cell lymphoma; OR
iv. High-grade B-cell lymphoma; OR
v. Diffuse large B-cell lymphoma arising from follicular lymphoma; OR
vi. Diffuse large B-cell lymphoma arising from nodal marginal zone lymphoma; OR
vii. Acquired immune deficiency syndrome (AIDS)-related B-cell lymphoma; OR
viii. Human herpes virus 8-positive diffuse large B-cell lymphoma; OR
ix. Post-transplant lymphoproliferative disorders; AND

D) The patient is ≥ 18 years of age; AND
E) Yescarta is prescribed by or in consultation with an oncologist; AND
F) Yescarta is being used for disease that is relapsed or refractory after two or more lines of systemic therapy; AND
G) The patient received lymphodepleting chemotherapy prior to Yescarta infusion; AND
H) The patient has not been previously treated with Yescarta or Kymriah® (tisagenlecleucel injection).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Yescarta has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

206. Re-treatment with Yescarta. Yescarta is for one time use, repeat dosing is not approvable.

207. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

670. Yescarta™ suspension for intravenous infusion [prescribing information]. Santa Monica, CA: Kite Pharma; May 2019.
671. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017;377(26):2531-2544.
672. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 1.2020 – January 22, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed April 17, 2020.
673. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on April 17, 2020. Search term: axicabtagene.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/24/2019
Annual Revision	**B-cell lymphoma:** Added approval criteria for diffuse large B-cell lymphoma arising from nodal marginal zone lymphoma. Revised criteria to not allow previous treatment with Yescarta.	04/29/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Zaltrap Prior Authorization Policy

- Zaltrap® (ziv-aflibercept injection for intravenous infusion – Regeneron Pharmaceuticals, Inc./Sanofi-Aventis)

REVIEW DATE: 09/23/2020

OVERVIEW

Zaltrap, a recombinant fusion protein, in combination with FOLFIRI (5-fluorouracil [5-FU], leucovorin, and irinotecan), is indicated for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) colon cancer guidelines (version 4.2020 – June 15, 2020)[2] and rectal cancer guidelines (version 6.2020 – June 25, 2020)[3] recommend Zaltrap as 1) primary treatment for patients with unresectable metachronous metastases and previous adjuvant FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) regimens within the past 12 months in combination with irinotecan OR with FOLFIRI, or 2) subsequent therapy after first progression of unresectable advanced or metastatic disease in combination with irinotecan or with FOLFIRI for disease not previously treated with an irinotecan-based regimen.[2-4] Both of these uses have a category 2A recommendation. In patients with advanced or metastatic disease, Zaltrap is not listed as an option for initial therapy. Zaltrap has a category 2B recommendation for use as adjuvant therapy, in combination with FLOFIRI or irinotecan for unresectable metachronous metastases that convert to resectable disease after primary treatment.

Zaltrap has only been effective when given with FOLFIRI in FOLFIRI-naïve patients.[2,3] There are no data suggesting activity of Zaltrap plus FOLFIRI in patients who progressed on FOLFIRI plus Avastin or vice versa. No data suggest that single-agent Zaltrap has therapeutic activity. The NCCN panel includes Zaltrap as a second-line option in combination with FOLFIRI or irinotecan only after progression on therapy that does not include irinotecan. The NCCN panels on colon and rectal cancers prefer bevacizumab over Zaltrap and Cyramza® (ramucirumab injection for intravenous use) as an anti-angiogenic agent based on toxicity and cost.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zaltrap. All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Zaltrap as well as the monitoring required for adverse events and long-term efficacy, approval requires Zaltrap to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zaltrap is recommended in those who meet the following criteria:

FDA-Approved Indications

228. Colon and Rectal Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):

30. Patient has advanced or metastatic disease; AND

31. Patient has been previously treated with an oxaliplatin- or fluoropyrimidine-containing regimen; AND

Note: Fluoropyrimidines include 5-fluorouracil (5-FU) and capecitabine.

32. Patient has not previously been treated with FOLFIRI; AND

Note: FOLFIRI includes 5-fluorouracil (5-FU), leucovorin, and irinotecan.

33. Zaltrap will be used in combination with 5-fluorouracil (5-FU) or capecitabine and/or irinotecan; AND

34. The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zaltrap is not recommended in the following situations:

208. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

674. Zaltrap® injection for intravenous infusion [prescribing information]. Bridgewater, NJ: Regeneron Pharmaceutical, Inc./sanofi-aventis U.S. LLC; June 2020.
675. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 4.2020 – June 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 16, 2020.
676. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (Version 6.2020 – June 25, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 16, 2020.
677. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 16, 2020. Search term: ziv-aflibercept.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	09/25/2019
Annual Revision	No criteria changes.	09/23/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Zepzelca Prior Authorization Policy

- Zepzelca™ (lurbinectedin injection – Jazz Pharmaceuticals)

REVIEW DATE: 07/01/2020

OVERVIEW

Zepzelca, an alkylating drug, is indicated for the treatment of metastatic small cell lung cancer in adults with disease progression on or after platinum-based chemotherapy.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) Small Cell Lung Cancer guidelines recommend Zepzelca as a single agent for the treatment of relapsed disease following a complete or partial response, or stable disease with initial treatment, or for the treatment of primary progressive disease.[2,3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zepzelca. All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Zepzelca as well as the monitoring required for adverse events and long-term efficacy, approval requires Zepzelca to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zepzelca is recommended in those who meet the following criteria:

FDA-Approved Indications

229. Small Cell Lung Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):

- **A)** Patient has metastatic disease; AND
- **B)** Patient has previously received platinum-based chemotherapy; AND
  Note: Examples of platinum medications include cisplatin and carboplatin.
- **C)** Zepzelca is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zepzelca is not recommended in the following situations:

209. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

678. Zepzelca injection for intravenous use [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals; June 2020.
679. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 9, 2020. Search term: lurbinectedin.
680. The NCCN Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 4.2020 – July 7, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 9, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/01/2020
Update	July 9, 2020: No criteria changes. Updated guidelines in Overview.	NA

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Other) – Jelmyto™ (mitomycin solution for pyelocalyceal administration – UroGen Pharma)

DATE REVIEWED: 05/20/2020

OVERVIEW

Jelmyto, an alkylating agent, is indicated for the treatment of adult patients with low-grade upper tract urothelial cancer (LG-UTUC).[1]

Dosing Information

Jelmyto is for pyelocalyceal use only.[1] The recommended dose is 4 mg/mL of mitomycin administered by ureteral catheter or a nephrostomy tube, with total instillation volume determined on volumetric measurements using pyelography, not to exceed 15 mL (60 mg of mitomycin). The dose is instilled once weekly for 6 weeks and in patients with a complete response 3 months after initiating Jelmyto, therapy can continue once a month for an additional 11 instillations.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for Bladder Cancer (Version 4.2020 – April 28, 2020) recommend Jelmyto as a primary treatment for upper urinary tract tumors.[2,3] Jelmyto is recommended following complete or near complete endoscopic resection or ablation of a low-grade, low volume, solitary tumor in patients not a candidate for or seeking definitive treatment with nephroureterectomy.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Jelmyto. All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Jelmyto as well as the monitoring required for adverse events and long-term efficacy, approval requires Jelmyto to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Jelmyto is recommended in those who meet the following criteria:

FDA-Approved Indications

230. Upper Tract Urothelial Cancer, Low-Grade. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** The patient is ≥ 18 years of age; AND
- **B)** The patient has non-metastatic disease; AND
- **C)** The patient has undergone endoscopic resection or ablation; AND
- **D)** Jelmyto is prescribed by or in consultation with an oncologist or urologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Jelmyto has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

210. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

681. Jelmyto™ for pyelocalyceal solution [prescribing information]. Princeton, NJ: UroGen Pharma; April 2020.
682. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (Version 4.2020 – April 28, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed April 29, 2020.
683. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on April 29, 2020. Search term: Jelmyto.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	05/20/2020

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Other) – Valrubicin Products Prior Authorization Policy
- Valrubicin solution for intravesical use (Valstar® – Endo Pharmaceuticals Solution, generics)

REVIEW DATE: 10/28/2020

OVERVIEW

Valrubicin (Valstar), an anthracycline topoisomerase inhibitor, is indicated for intravesical therapy of BCG-refractory **carcinoma *in situ* (CIS) of the urinary bladder** in patients for whom immediate cystectomy would be associated with unacceptable morbidity or mortality.[1]

Guidelines

The National Comprehensive Cancer Network guidelines for **bladder cancer** (version 6.2020 – July 16, 2020) recommend intravesical valrubicin in the event of a Bacillus Calmette-Guerin (BCG) shortage and for recurrent or persistent BCG-refractory carcinoma *in situ* (Tis) disease.[2,3]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of valrubicin. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because of the specialized skills required for evaluation and diagnosis of patients treated with valrubicin as well as the monitoring required for adverse events and long-term efficacy, approval requires valrubicin to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of valrubicin is recommended in those who meet the following criteria:

FDA-Approved Indications

231. Bladder Cancer. Approve for 2 months if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets one of the following (i or ii):
  - **i.** Patient has recurrent or persistent Bacillus Calmette-Guerin (BCG)-refractory carcinoma; OR
  - **ii.** According to the prescriber, valrubicin will be used due to a Bacillus Calmette-Guerin (BCG) shortage; AND
- **C)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of valrubicin is not recommended in the following situations:

211. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

684. Valstar solution [prescribing information]. Malvern, PA: Endo Pharmaceuticals Solutions; October 2019.
685. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 13, 2020. Search term: valrubicin.
686. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (Version 6.2020 – July 16, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 13, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/16/2019
Annual Revision	No criteria changes.	10/28/2020

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmic for Dry Eye Disease – Cyclosporine Products Prior Authorization Policy
- Cequa™ (cyclosporine topical solution – Sun Pharmaceuticals)
- Restasis and Restasis Multidose™ (cyclosporine topical emulsion – Allergan)

REVIEW DATE: 08/19/2020

OVERVIEW

Restasis (cyclosporine topical emulsion), an immunosuppressive agent, is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with

keratoconjunctivitis sicca.[1,2] The safety and efficacy of Restasis have not been established in pediatric patients < 16 years of age.

Cequa is a topical solution of cyclosporine, with the same active ingredient and mechanism as Restasis.[3] Although Cequa is approved for patients ≥ 18 years of age per product labeling, it has the same active chemical moiety as Restasis, which is approved in patients ≥ 16 years of age.[1-3] Cequa has a novel formulation in which the hydrophobic cyclosporine molecules are encased in nanomicelles with a hydrophilic exterior.[4] This facilitates crossing of the corneal barrier and penetration of the aqueous humor to reach ocular tissues.

Other Uses with Supportive Evidence

Systemic Inflammatory Diseases

Patients with primary Sjögren syndrome have nonclassifiable systemic disease, whereas patient with secondary Sjögren syndrome have a distinct autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus, or scleroderma. A 2010 systematic review of randomized controlled trials for the treatment of primary Sjögren syndrome found topical cyclosporine to be effective for moderate or severe dry eye symptoms.[7]

Ocular Surface Diseases

There are some efficacy data to support the off-label use of topical cyclosporine in the treatment of immune-mediated ocular surface diseases such as ocular rosacea and atopic keratoconjunctivitis.[6,8-11] A review article noted that dosing of Restasis at a frequency greater than twice daily (BID) regimen may be beneficial for patients with severe dry eye disease, such as ocular graft versus host disease (GVHD), if they do not initially respond to the BID regimen.[12] Also, it has been suggested that initiation of topical cyclosporine prior to bone marrow transplantation may reduce inflammatory response in the lacrimal gland and could reduce dry eye symptoms post-transplant.

Guidelines

The American Academy of Ophthalmology (AAO) published Preferred Practice Pattern® (2018) for the treatment of dry eye syndrome.[5] The AAO classifies dry eye as mild, moderate, or severe, based on signs and symptoms of the disease. Treatment recommendations of dry eye disease are listed in a four step progression but specific therapies may be chosen from any category regardless of the level of disease severity, depending on provider experience and patient preference. Topical nonglucocorticoid immunomodulatory drugs (such as cyclosporine) are staged as a Step 2 recommendation within the guidelines. The AAO recommends the use of topical cyclosporine as one of the treatment options for Sjögren syndrome. The AAO states that topical cyclosporine may be useful in some patients with posterior blepharitis, in active ocular GVHD, and as adjunctive treatment in atopic/vernal conjunctivitis.[13-14]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Restasis and Cequa. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Restasis and Cequa is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Dry Eye Conditions due to Ocular Inflammation Associated with Keratoconjunctivitis Sicca (e.g., dry eye syndrome or dry eye disease).** Approve for 3 years if the patient is ≥ 16 years of age.

Other Uses with Supportive Evidence

2. **Dry Eye Conditions due to Systemic Inflammatory Diseases (e.g., Sjögren syndrome, rheumatoid arthritis, systemic lupus erythematosus).** Approve for 3 years if the patient is ≥ 16 years of age.

3. **Dry Eye Conditions due to Ocular Surface Diseases (e.g., ocular rosacea, atopic keratoconjunctivitis, acute corneal graft rejection, blepharitis, herpetic stromal keratitis, conjunctival graft versus host disease).** Approve for 3 years if the patient is ≥ 16 years of age.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Restasis and Cequa is not recommended in the following situations:

212. **Concomitant use with Xiidra™ (lifitegrast ophthalmic solution).** There are no data to support the concomitant use of Restasis or Cequa and Xiidra.

213. **Concomitant use of Cyclosporine Products.** There is no evidence to support additive efficacy of combining Restasis and Cequa.

214. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

448. Restasis® ophthalmic emulsion 0.05% [prescribing information]. Irvine, CA: Allergan, Inc.; July 2017.
449. Restasis Multidose™ ophthalmic emulsion 0.05% [prescribing information]. Irvine, CA: Allergan; July 2017.
450. Cequa™ ophthalmic solution [prescribing information]. Cranbury, NJ: Sun Pharmaceutical Industries; August 2018.
451. Data on file. Cequa® Product Dossier. Based on AMCP guidelines for formulary submission. Sun Pharmaceutical Industries, Inc.; August 2018.
452. American Academy of Ophthalmology cornea/external disease panel. Preferred practice pattern® guidelines. Dry eye syndrome. San Francisco, CA: American Academy of Ophthalmology; 2018. Available at: www.aao.org/ppp. Accessed on August 11, 2020.
453. Yagci A, Gurdal C. The role and treatment of inflammation in dry eye disease. *Int Ophthalmol*. 2014;34(6):1291-1301.
454. Ramos-Casals M, Tzioufas AG, Stone JH, et al. Treatment of primary Sjogren syndrome – a systematic review. *JAMA*. 2010;304:452-460.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No change to criteria.	08/01/2018
Selected Revision	Policy name changed to *Ophthalmic for Dry Eye Disease – Cyclosporine Products PA Policy*. Added Cequa to policy. **Concomitant use of Cyclosporine Products:** Added to Conditions Not Recommended for Approval.	10/17/2018

Update	Under "Recommended Authorization Criteria", clarified language that coverage is recommended for Restasis or Cequa in those who meet the criteria.	12/06/2018
Annual Revision	No criteria changes.	08/28/2019
Annual Revision	For all approval conditions, the requirement of an optometrist or ophthalmologist in the criteria was removed.	08/19/2020

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmic for Dry Eye Disease – Eysuvis Prior Authorization Policy

- Eysuvis™ (loteprednol etabonate 0.25% ophthalmic suspension – Kala Pharmaceuticals)

REVIEW DATE: 12/09/2020

OVERVIEW

Eysuvis, an ophthalmic corticosteroid, is indicated for the **short-term (up to 2 weeks) treatment of the signs and symptoms of dry eye disease**.[1]

Eysuvis is a topical, anti-inflammatory, nanoparticle suspension of loteprednol etabonate with proprietary mucus-penetrating particle technology synthesized through structural modifications of prednisolone-related compounds so that it will undergo a predictable transformation to an inactive metabolite.[1,2] Eysuvis inhibits the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation.

Guidelines

Eysuvis is not addressed in guidelines. The American Academy of Ophthalmology (AAO) published a Preferred Practice Pattern® (2018) for the treatment of dry eye syndrome.[3] Some risk factors for dry eye syndrome include aging, female gender, decrease in supportive factors such as androgen hormones, radiation therapy, surgeries that disrupt the trigeminal afferent sensory nerves (e.g., laser-assisted in situ keratomileusis [LASIK]) or systemic inflammatory conditions such as rheumatoid arthritis. For mild dry eyes, education and environmental modifications, artificial tear solutions and eyelid therapy (warm compresses and eyelid scrubs) are listed as some of the treatment options. Guidelines noted a commercially available loteprednol etabonate 0.5% was used in a prospective, randomized study for a 2-week period. The study found a favorable effect in patients' dry eye symptoms and conjunctival hyperemia findings, but not in ocular surface staining, Schirmer test results, or use of artificial tears.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Eysuvis. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Eysuvis is recommended in those who meet the following criteria:

FDA-Approved Indications

232. Dry Eye Disease (Short-term Treatment). Approve for 1 month if the patient meets the following (A and B):

A) Patient has tried artificial tears; AND

B) Patient has tried one other formulation of ophthalmic loteprednol etabonate.
Note: Examples of other ophthalmic loteprednol etabonate formulations include Alrex® 0.2% suspension, Inveltys® 1% suspension, loteprednol etabonate 0.5% suspension (Lotemax®, generics), Lotemax® 0.5% gel, Lotemax® SM 0.38% gel, and Lotemax® 0.5% ointment.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Eysuvis is not recommended in the following situations:

215. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

687. Eysuvis® ophthalmic suspension [prescribing information]. Watertown, MA: Kala Pharmaceuticals; October 2020.
688. Korenfeld M, Nichols KK, Goldberg D, et al. Safety of KPI-121 ophthalmic suspension 0.25% in patients with dry eye disease: a pooled analysis of 4 multicenter, randomized, vehicle-controlled studies. *Cornea*. 2020 August 19. [Online ahead of print].
689. American Academy of Ophthalmology cornea/external disease panel. Preferred Practice Pattern® Guidelines. Dry eye syndrome. San Francisco, CA: American Academy of Ophthalmology; 2018. Available at: www.aao.org/ppp. Accessed on October 29, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/09/2020

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmic for Dry Eye Disease – Lacrisert Prior Authorization Policy

- Lacrisert® (hydroxypropyl cellulose ophthalmic insert – Bausch & Lomb)

REVIEW DATE: 12/02/2020

OVERVIEW

Lacrisert, an ophthalmic insert made of hydroxypropyl cellulose, is indicated for the following uses:[1]

- **Decreased corneal sensitivity**.
- **Exposure keratitis**.
- **Moderate to severe dry eye syndromes**, including keratoconjunctivitis sicca.
- **Recurrent corneal erosions**.

Lacrisert acts to stabilize and thicken the precorneal tear film and prolong the tear film breakup time which is usually accelerated in patients with dry eye states.[1] Lacrisert also acts to lubricate and protect the eye. Lacrisert usually reduces the signs and symptoms resulting from moderate to severe dry eye syndromes, such as conjunctival hyperemia,

corneal and conjunctival staining with rose bengal, exudation, itching, burning, foreign body sensation, smarting, photophobia, dryness and blurred or cloudy vision. Progressive visual deterioration which occurs in some patients may be slowed, halted, or sometimes reversed.

Guidelines

The American Academy of Ophthalmology (AAO) published Preferred Practice Pattern® (2018) for the treatment of dry eye syndrome.[2] The AAO classifies dry eye as mild, moderate, or severe, based on signs and symptoms of the disease. Treatment recommendations of dry eye disease are listed in a four step progression but specific therapies may be chosen from any category regardless of the level of disease severity, depending on provider experience and patient preference. Slow-release hydroxypropyl cellulose inserts are recommended within the guidelines for moderate dry eye as occasionally helpful for patients who are unable to apply artificial tears.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lacrisert. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lacrisert is recommended in those who meet the following criteria:

FDA-Approved Indications

233. Ocular Conditions Associated with Moderate to Severe Dry Eye (e.g., decreased corneal sensitivity, dry eye syndrome, exposure keratitis, keratoconjunctivitis sicca, recurrent corneal erosions). Approve for 1 year if the patient has tried artificial tears.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lacrisert is not recommended in the following situations:

216. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

690. Lacrisert® ophthalmic insert [prescribing information]. Bridgewater, NJ: Bausch & Lomb; October 2019.
691. American Academy of Ophthalmology cornea/external disease panel. Preferred practice pattern® guidelines. Dry eye syndrome. San Francisco, CA: American Academy of Ophthalmology; 2018. Available at: www.aao.org/ppp. Accessed on November 17, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/02/2020

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmic for Dry Eye Disease – Xiidra Prior Authorization Policy

- Xiidra™ (lifitegrast ophthalmic solution – Novartis)

REVIEW DATE: 08/19/2020

OVERVIEW
Xiidra, a lymphocyte function-associated antigen-1 (LFA-1) antagonist, is indicated for the treatment of the signs and symptoms of dry eye disease.[1]

Guidelines
The American Academy of Ophthalmology (AAO) published Preferred Practice Pattern® (2018) for the treatment of dry eye syndrome.[2] The AAO classifies dry eye as mild, moderate, or severe, based on signs and symptoms of the disease. Treatment recommendations of dry eye disease are listed in a four step progression but specific therapies may be chosen from any category regardless of the level of disease severity, depending on provider experience and patient preference. Topical LFA-1 antagonist drugs (such as lifitegrast) are staged as a Step 2 recommendation within the guidelines.

POLICY STATEMENT
Prior authorization is recommended for prescription benefit coverage of Xiidra. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Xiidra is recommended in those who meet the following criteria:

FDA-Approved Indications

~~73.~~70. **Dry Eye Disease (e.g., dry eye syndrome).** Approve for 3 years if the patient is ≥ 18 years of age.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Xiidra is not recommended in the following situations:

217. **Concomitant use with an ophthalmic cyclosporine product (Restasis®, Cequa™).** There are no data to support the concomitant use of Restasis or Cequa and Xiidra.

218. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

462. Xiidra™ ophthalmic solution [prescribing information]. East Hanover, NJ: Novartis; July 2020.
463. American Academy of Opthalmology Cornea/External Diseases Panel. Preferred Practice Pattern® guidelines. Dry eye syndrome. San Francisco, CA: American Academy of Ophthalmology; 2018. Available at: www.aao.org/ppp. Accessed on August 11, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	No criteria changes.	08/01/2018
Annual revision	No criteria changes.	08/28/2019
Annual Revision	**Dry Eye Disease (e.g., dry eye syndrome):** The requirement of an optometrist or ophthalmologist in the criteria was removed. **Concomitant use with Restasis®:** Cequa was added as an ophthalmic cyclosporine product not recommended for use with Xiidra.	08/19/2020

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmic Prostaglandins

- Bimatoprost 0.03% ophthalmic solution (generic to discontinued Lumigan® 0.03% ophthalmic solution) – Lupin Pharmaceuticals, others
- Lumigan® (bimatoprost 0.01% ophthalmic solution – Allergan)
- Rocklatan™ (netarsudil 0.02%/latanoprost 0.005% ophthalmic solution – Aerie Pharmaceuticals)
- Travatan® Z (travoprost 0.004% ophthalmic solution [benzalkonium chloride-free] – Alcon, generics)
- Vyzulta™ (latanoprostene bunod 0.024% ophthalmic solution – Bausch & Lomb)
- Xalatan® (latanoprost 0.005% ophthalmic solution – Pharmacia & Upjohn, generics)
- Xelpros™ (latanoprost 0.005% ophthalmic emulsion – Sun Pharmaceuticals)
- Zioptan® (tafluprost 0.0015% ophthalmic solution – Merck)

DATE REVIEWED: 04/22/2020

OVERVIEW

Ophthalmic prostanoids include prostaglandin analogues (latanoprost, travoprost 0.004% ophthalmic solution (generic to Travatan Z), Vyzulta, and Zioptan,) and prostamides (Lumigan and bimatoprost 0.03% [generic to discontinued Lumigan 0.03%]). All of the ophthalmic products included in this policy are single-entity products, except Rocklatan, which contains netarsudil, a Rho kinase inhibitor, and latanoprost. All of these are indicated for the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension.[1-8] Bimatoprost 0.03% ophthalmic solution is also marketed as Latisse®, indicated to treat hypotrichosis of the eyelashes by increasing their growth including length, thickness, and darkness.[9] (Note: Latisse is not included in this PA Policy).

Glaucoma, a disease that damages the eye's optic nerve, is the leading cause of blindness in people > 60 years old.[10] Reduction of IOP, regardless of the pretreatment IOP, reduces the risk of disease progression.[11] In addition, IOP reduction may prevent the onset to early glaucoma in patients with ocular hypertension.

Normal-tension glaucoma is a form of open-angle glaucoma (OAG) characterized by glaucomatous optic neuropathy in patients with IOP measurements consistently < 21 mmHg.[12] According to the Glaucoma Research Foundation, normal-tension glaucoma is also referred to as low-tension glaucoma or normal-

pressure glaucoma.[13] Additionally, the American Academy of Ophthalmology (AAO) guidelines on primary open-angle glaucoma include normal-tension glaucoma in the recommendations for care, stating that lowering IOP reduces the risk of developing primary open-angle glaucoma and slows the progression of primary open-angle glaucoma, including normal-tension open-angle glaucoma.[11]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of ophthalmic prostaglandins. An age edit for patients < 60 years of age is used to monitor for appropriate use and to screen for cosmetic use. Prescription benefit coverage of these products for cosmetic conditions is not recommended. All approvals are provided for 3 years unless otherwise noted below. Prior authorization and prescription benefit coverage is not recommended for Latisse.

Automation: If the patient is < 60 years of age and does not have a history of one ophthalmic glaucoma agent within the 130-day look-back period, coverage will be determined by prior authorization criteria.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of ophthalmic prostaglandins is recommended in those who meet the following criteria:

FDA-Approved Indication

33. Reduction of Intraocular Pressure (IOP) in Patients with Open Angle Glaucoma or Ocular Hypertension. Approve.
Note: Open angle glaucoma includes normal-tension glaucoma, which is also referred to as low-tension glaucoma or normal-pressure glaucoma.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of the ophthalmic prostaglandins is not recommended in the following circumstances. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

285. Cosmetic Conditions (e.g., eyelash growth). Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical pharmacy benefit.

286. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

12. Xalatan® 0.005% ophthalmic solution [prescribing information]. New York, NY: Pharmacia & Upjohn Co, Division of Pfizer Inc; April 2017.
13. Lumigan® 0.01% ophthalmic solution [prescribing information]. Irvine, CA: Allergan, Inc.; July 2017.
14. Travatan® Z 0.004% ophthalmic solution [prescribing information]. Fort Worth, TX: Alcon Laboratories, Inc.; September 2017.
15. Zioptan® 0.0015% ophthalmic solution [prescribing information]. Akorn, Inc: Lake Forest, IL; November 2018.
16. Vyzulta™ [prescribing information]. Bridgewater, NJ: Bausch & Lomb, division of Valeant Pharmaceuticals North America LLC; May 2019.
17. Bimatoprost 0.03% ophthalmic solution [prescribing information]. Baltimore, MD: Lupin Pharmaceuticals, Inc.; February 2018.

18. Rocklatan™ [prescribing information]. Irvine, CA: Aerie Pharmaceuticals, Inc; March 2019.
19. Xelpros™ [prescribing information]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc; September 2018.
20. Latisse® [prescribing information]. Irvine, CA: Allergan, Inc.; July 2017.
21. Boyd K. Glaucoma. Available at: https://www.aao.org/eye-health/diseases/what-is-glaucoma. Accessed on March 23, 2020.
22. Prum BE, Rosenberg LF, Gedde SJ, et al. Preferred practice pattern: primary open-angle glaucoma. The American Academy of Ophthalmology. 2015. Available at: http://www.aao.org/guidelines-browse?filter=preferredpracticepatterns. Accessed on March 23, 2020.
23. Stein JD, Challa P. Diagnosis and Treatment of Normal-Tension Glaucoma. *EyeNet Magazine*. 2007 February. Available at: https://www.aao.org/eyenet/article/diagnosis-treatment-of-normal-tension-glaucoma. Accessed on March 23, 2020.
24. Glaucoma Research Foundation. Normal-Tension Glaucoma. Last reviewed on October 29, 2017. Available at: https://www.glaucoma.org/glaucoma/normal-tension-glaucoma.php. Accessed on March 23, 2020.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual revision	No criteria changes.	04/25/2018
Annual revision	Add Rocklatan and Xelpros to the policy. Removed Rescula (obsolete as of 03-2016). No criteria changes.	04/10/2019
Annual revision	No criteria changes. Removed Travatan (travoprost 0.004% ophthalmic solution, generics) – obsolete for > 3 years	04/22/2020

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Durysta™ (bimatoprost implant, for intracameral administration – Allergan)

DATE REVIEWED: 04/22/2020

OVERVIEW

Durysta, a prostaglandin analog, is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.[1]

Glaucoma, a disease that damages the eye's optic nerve, is the leading cause of blindness in people > 60 years of age.[2] Reduction of IOP, regardless of the pretreatment IOP, reduces the risk of disease progression.[3] In addition, IOP reduction may prevent the onset of early glaucoma in patients with ocular hypertension.

Ophthalmic prostaglandins, beta-blockers, alpha-agonist (brimonidine), carbonic anhydrase inhibitors, rho kinase inhibitor (netarsudil), and fixed combination products are used to treat glaucoma.[3,4] The choice of product is influenced by potential cost, adverse event profile, dosing schedule, and the degree of pressure lowering needed.[3]

Dosing Considerations

Durysta, a biodegradable implant, is given as a single intracameral administration.[1] Durysta should not be re-administered to an eye that was previously treated with Durysta.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Durysta. Because of the specialized skills required for evaluation and diagnosis of patients treated with Durysta, as well as the monitoring required for adverse events and long-term efficacy, approval requires Durysta to be prescribed by, or in consultation with, a physician who specializes in the condition being treated. All approvals are provided for one implant per treated eye (i.e., one implant per treated eye; maximum of two implants per patient). Note that a 1-month (30 days) approval duration is applied to allow for the one-time treatment of one or both eye(s).

Automation: None

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Durysta is recommended in those who meet the following criteria:

FDA-Approved Indications

6. Reduction of Intraocular Pressure (IOP) in Patients with Open-Angle Glaucoma or Ocular Hypertension. Approve for a one-time use in each treated eye (i.e., one implant per treated eye; a total of two implants per patient) if the patient meets ALL of the following criteria (A, B, C, D, and E):

- **A)** The patient is ≥ 18 years of age; AND
- **B)** The patient is not receiving re-treatment of eye(s) previously treated with Durysta; AND
- **C)** The patient meets the following criteria (i and ii):
  - **i.** The patient has tried at least two ophthalmic prostaglandins (either as monotherapy or as concomitant therapy) for the treatment of open-angle glaucoma or ocular hypertension.
    Note: Examples of ophthalmic prostaglandins include bimatoprost 0.03% ophthalmic solution, latanoprost 0.005% ophthalmic solution, travoprost 0.004% ophthalmic solution; Lumigan® (bimatoprost 0.01% ophthalmic solution), Vyzulta® (latanoprostene bunod 0.024% ophthalmic solution), Xelpros™ (latanoprost 0.005% ophthalmic emulsion), and Zioptan® (tafluprost 0.0015% ophthalmic solution); AND
  - **ii.** The patient has tried at least two ophthalmic products (either as monotherapy or as concomitant therapy) from two different pharmacological classes for the treatment of open-angle glaucoma or ocular hypertension.
    Note: Examples of pharmacological classes of ophthalmic products for the treatment of open-angle glaucoma or ocular hypertension include beta-blockers, alpha-agonist (brimonidine), carbonic anhydrase inhibitors, and rho kinase inhibitor (netarsudil); AND
- **D)** For each of the ophthalmic medications that were tried, the patient meets ONE of the following criteria (i or ii):
  - **i.** The patient has had inadequate efficacy to the previously-tried ophthalmic products, according to the prescriber; OR
  - **ii.** The patient has experienced adverse event(s) severe enough to warrant discontinuation of the previously-tried ophthalmic products, according to the prescriber; AND
- **E)** Durysta is prescribed by, or in consultation with, an ophthalmologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Durysta has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

219. Re-Treatment of Previously-Treated Eye(s). Durysta is approved for a one-time use in each treated eye. Repeat administration in previously treated eye(s) is not approvable.

220. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

360. Durysta™ [prescribing information]. Madison, NJ: Allergan USA, Inc; March 2020.
361. Boyd K. Glaucoma. Available at: https://www.aao.org/eye-health/diseases/what-is-glaucoma . Accessed on March 23, 2020.
362. Prum BE, Rosenberg LF, Gedde SJ, et al. Preferred practice pattern: primary open-angle glaucoma. The American Academy of Ophthalmology. 2015. Available at: http://www.aao.org/guidelines-browse?filter=preferredpracticepatterns. Accessed on March 23, 2020.
363. Facts and Comparisons® Online. Wolters Kluwer Health, Inc.; 2020. Available at: http://online.factsandcomparisons.com/login.aspx?url=/index.aspx&qs=. Accessed on March 23, 2020. Search term: netarsudil.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/22/2020

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Luxturna Prior Authorization Policy

- Luxturna™ (voretigene neparvovec-rzyl intraocular suspension for subretinal injection – Spark Therapeutics)

REVIEW DATE: 02/17/2021

OVERVIEW

Luxturna, an adeno-associated virus vector-based gene therapy, is indicated for the treatment of patients with **confirmed biallelic human retinal pigment epithelial 65 kDa protein (RPE65) mutation-associated retinal dystrophy**.[1] Patients must have viable retinal cells as determined by the treating physician(s).

Luxturna is made up of a live, non-replicating adeno-associated virus serotype 2 which has been genetically modified to express the human RPE65 gene.[1] Luxturna is designed to deliver a normal copy of the gene encoding RPE65 to cells of the retina in patients with reduced or absent levels of biologically active RPE65.

Disease Overview

Inherited retinal dystrophies are a broad group of genetic retinal disorders that are associated with progressive visual dysfunction.[2] RPE65 mutation-associated retinal dystrophy is associated with at least 125 discrete gene mutations and affects 1,000 to 2,000 patients in the US.[2,3] Mutations in the RPE65 gene lead to reduced or absent levels of RPE65 isomerohydrolase activity.[1] The absence of RPE65 leads to the accumulation of toxic precursors, damage to RPE-producing cells, and, over time, damage to photoreceptors, progressing to near total blindness in most patients. The retinal anatomy is preserved for a relatively long period, and supplying the missing enzyme can result in restoration of the visual cycle and improvement in vision.[3]

Dosing Information

The recommended dose of Luxturna for each eye is 1.5×10^{11} vector genomes (vg) administered once per eye by subretinal injection.[1] After completing a vitrectomy (removal of the vitreous gel that fills the eye cavity) and under direct visualization, a small amount of Luxturna is injected slowly until an initial subretinal bleb is observed; the remaining volume is then injected slowly until the total 0.3 mL is delivered. Luxturna should be injected into each eye on separate days within a close interval, but no less than 6 days apart. Luxturna is not recommended for patients < 12 months of age, because the retinal cells are still undergoing cell proliferation, and Luxturna would potentially be diluted or lost during cell proliferation.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Luxturna. Because of the specialized skills required for evaluation and diagnosis of patients treated with Luxturna as well as the specialized training required for administration of Luxturna, approval requires Luxturna to be prescribed by a physician who specializes in the condition being treated. All approvals are provided for one injection

per eye. Note: A 1-month (30 days) approval duration is applied to allow for the one-time treatment of both eyes.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Luxturna is recommended in those who meet the following criteria:

FDA-Approved Indications

3. **Biallelic Human Retinal Pigment Epithelial 65 kDa Protein (RPE65) Mutation-Associated Retinal Dystrophy.** Approve for one-time treatment course (i.e., a total of two injections, one injection in each eye) if the patient meets the following criteria (A, B, C, D, and E):
   - **G)** According to the prescribing physician, the patient has a genetically-confirmed diagnosis of biallelic RPE65 mutation-associated retinal dystrophy; AND
   - **H)** Patient is ≥ 12 months of age; AND
   - **I)** Luxturna is administered by a retinal specialist; AND
   - **J)** Patient must have viable retinal cells as determined by the treating physician; AND
   - **K)** Patient is not receiving re-treatment of eye(s) previously treated with Luxturna.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Luxturna is not recommended in the following situations:

287. Re-treatment of previously treated eye(s). Luxturna is for one time use in each eye. Repeat dosing in previously treated eye(s) is not approvable.

288. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

15. Luxturna™ subretinal injection [prescribing information]. Philadelphia, PA: Spark Therapeutics, Inc.; December 2019.
16. FDA news release. FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss. Published on: December 19, 2017. Page last updated: March 16, 2018. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm589467.htm. Accessed on February 9, 2021.
17. Spark Therapeutics. Luxturna™ (voretigene neparvovec). FDA Advisory Committee Briefing Document. Meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee. Meeting date: October 12, 2017. Available at: https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/bloodvaccinesandotherbiologics/cellulartissueandgenetherapiesadvisorycommittee/ucm579300.pdf. Accessed on February 9, 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Criteria was revised to add "patient is not receiving re-treatment of eye(s) previously treated with Luxturna". "Re-treatment of previously treated eye(s)" was also added as a Condition Not Recommended for Approval. Previously, this was addressed only the noted duration of "one-time treatment".	02/20/2019
Annual Revision	No criteria changes.	02/19/2020
Annual Revision	No criteria changes.	02/17/2021

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Oxervate Prior Authorization Policy

- Oxervate™ (cenegermin-bkbj ophthalmic solution – Dompé farmaceutici S.p.A)

REVIEW DATE: 11/18/2020

OVERVIEW

Oxervate, a recombinant human nerve growth factor, is indicated for the treatment of **neurotrophic keratitis**.[1]

Disease Overview

Neurotrophic keratitis, a rare degenerative disease, is characterized by corneal epithelium breakdown, impairment of corneal healing, and development of corneal ulceration, melting, and perforation.[2-4] Corneal epithelial cells release various neurotrophic growth factors, including nerve growth factors, which are important in maintaining the integrity and function of the ocular surface and in stimulating both epithelial and nerve fiber proliferation and survival.[5,6] When corneal sensory innervation is impaired, reduction of both protective reflexes and trophic neuromodulators essential for the vitality, metabolism, and wound healing of the ocular surface tissues results. *In vivo* studies have shown that increasing nerve growth factor concentration after injury can accelerate healing.[3,6]

Guidelines/Recommendations

Prior to the approval of Oxervate, there were no approved pharmacologic therapies for the treatment of neurotrophic keratitis.[2] If neurotrophic keratitis is left untreated, the condition can progress to anatomical loss of the eye; even with treatment, loss of vision is common.[5] Current treatment options are supportive and do not improve the speed of healing. Treatment should target corneal sensory innervation impairment to restore corneal integrity; treatment goals are to stop progression and reverse damage from neurotrophic keratitis.

Regardless of disease severity/stage, all topical medications should be discontinued to avoid topical drug toxicity on the corneal epithelium.[3,4] Additionally, preservative-free artificial tears should be used to improve lubrication. Prophylactic topical antibiotics can be considered to prevent superinfections. Associated ocular surface disease, such as exposure keratitis, dry eye, or limbal stem cell deficiency, should be treated to improve the prognosis of neurotrophic keratitis. Therapeutic contact lenses can be used to promote corneal healing.[6] Surgical interventions are reserved for refractory cases.[3,4.6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Oxervate. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Oxervate as well as the monitoring required for adverse events and long-term efficacy, approval requires Oxervate to be prescribed by, or in consultation with, a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Oxervate is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Neurotrophic Keratitis.** Approve for 2 months if Oxervate is prescribed by or in consultation with an ophthalmologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Oxervate is not recommended in the following situations:

11. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

364. Oxervate™ ophthalmic solution [prescribing information]. L'Aquila, Italy: Domp farmaceutici S.p.A; October 2019.
365. Oxervate. FDA Clinical Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761094Orig1s000TOC.cfm. Accessed on November 11, 2020.
366. Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of the corneal nerve. *J Cell Physiol*. 2017;232:717-724.
367. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthamol*. 2018;8:571-579.
368. Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Progress in Retinal and Eye Research*. 2018;16:107-131.
369. Vesura P, Giannaccare G, Pellegrini M, et al. Neurotrophic keratitis: current challenges and future prospects. *Eye and Brain*. 2018;10:37-45.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/31/2018
Annual Revision	No criteria changes.	11/06/2019
Annual Revision	No criteria changes.	11/18/2020

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Tepezza Prior Authorization Policy

- Tepezza™ (teprotumumab injection for intravenous use – Horizon Therapeutics)

REVIEW DATE: 01/13/2021

OVERVIEW

Tepezza, an insulin-like growth factor-1 receptor (IGF-1R) antagonist, is indicated for the treatment of **thyroid eye disease**.[1]

Disease Overview

Thyroid eye disease is a progressive, vision-threatening autoimmune inflammatory disease of the eye and orbital tissues with predominant features of fibrosis and adipogenesis.[2] It is also recognized in literature as Graves' ophthalmopathy, Graves' orbitopathy, thyroid-associated ophthalmopathy, and thyroid orbitopathy. Thyroid eye disease is most commonly related with Graves' disease, it can also develop in patients with other thyroid diseases (e.g., Hashimoto's thyroiditis) and has a higher prevalence in women than men (16 per 100,000 vs. 3 per 100,000, respectively).[3] In active disease, orbital fibroblasts appear responsible for soft tissue enlargement by expressing potential pathogenic autoantigens, such as thyrotropin receptor and IGF-1R.[2] Activation of orbital fibroblasts leads to increased hyaluronic acid production, proinflammatory cytokine synthesis, and enhanced differentiation into either myofibroblasts or adipocytes. These processes result in inflammation, enlargement of extraocular muscles and expansion of orbital tissue and fat, which in turn cause forward displacement of the eye, resulting in proptosis and inflammation.[4] The degree of severity can be staged as mild, moderate-to-severe, or sight-threatening, following

quantitative assessment of lid aperture width, proptosis measurement, diplopia score, degrees of abduction in eye muscle movement, examination of the cornea for evidence of exposure keratitis or ulceration, and assessment of optic nerve function.

Dosing Information

The recommended dose is 10 mg/kg administered by intravenous (IV) infusion for the initial dose, followed by 20 mg/kg by IV infusion administered once every 3 weeks for seven additional doses.[1] Data for retreatment with Tepezza is still ongoing and are not yet available.[5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tepezza. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tepezza as well as the monitoring required for adverse events and long-term efficacy, approval requires Tepezza to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tepezza is recommended in those who meet the following criteria:

FDA-Approved Indications

234. Thyroid Eye Disease. Approve for 6 months if the patient meets the following criteria (A, B, C, and D):

Note: Thyroid Eye Disease is also recognized as Graves' ophthalmopathy, Graves' orbitopathy, thyroid-associated ophthalmopathy, and thyroid orbitopathy.

A) Patient is ≥ 18 years of age; AND

B) Patient has been assessed as having active disease of at least moderate severity based on signs and symptoms (e.g., the degree of inflammation, degree of proptosis, presentation of diplopia, etc.), according to the prescriber; AND

C) Patient has not received 8 doses (total) of Tepezza per treated eye; AND

Note: The maximum recommended treatment is for 8 doses per affected eye. For a patient who has started therapy but has not completed 8 doses, approve the number of doses required for the patient to receive a total of 8 doses per affected eye.

D) The medication is prescribed by or in consultation with an ophthalmologist, endocrinologist, or a physician who specializes in thyroid eye disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tepezza is not recommended in the following situations:

221. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

692. Tepezza injection [prescribing information]. Lake Forest, IL: Horizon Therapeutics; January 2020.
693. Horizon. Teprotumumab for injection. Breifing document for the Food and Drug Administration Dermatologic and Ophthalmic Drugs Advisory Committee. Meeting Date: December 13, 2019. Available at: https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-public-participation-information-december-13-2019-meeting-dermatologic-and-ophthalmic-drugs#event-information. Accessed on January 6, 2021.
694. Bartley GB, Fatourechi V, Kadrmas EF, Jacobsen SJ, Ilstrup DM, Garrity JA, Gorman CA. Clinical features of Graves' ophthalmopathy in an incidence cohort. Am J Ophthalmol 1996;121(3):284-290.
695. Shan S, Douglas R. The pathophysiology of thyroid eye disease. J Neuroophthalmol. 2014 Jun;34(2):177-85.
696. U.S. National Library of Medicine. Available at: Treatment of Graves' Orbitopathy to Reduce Proptosis With Teprotumumab Infusions in an Open-Label Clinical Extension Study - Full Text View - ClinicalTrials.gov. Accessed on January 6, 2021.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/29/2020
Annual Revision	**Thyroid Eye Disease:** Criteria was revised to add "Patient has not received 8 doses (total) of Tepezza per treated eye". For a patient who has started therapy but has not completed 8 doses, the number of doses required for the patient to receive a total of 8 doses per affected eye are approved.	01/13/2021

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Upneeq Prior Authorization Policy

- Upneeq™ (oxymetazoline hydrochloride 0.1% ophthalmic solution – Osmotica/RVL Pharmaceuticals)

REVIEW DATE: 08/19/2020

OVERVIEW

Upneeq, an alpha-adrenergic agonist, is indicated for the treatment of acquired blepharoptosis in adults.[1]

Disease Overview and Clinical Efficacy

Blepharoptosis, also known as ptosis, is an abnormal low-lying upper eyelid margin, which can decrease or even completely occlude vision.[2] Two vehicle-controlled pivotal studies were conducted; results are not published at this time.[3,4] The primary outcome of change in Leicester Peripheral Field Test (a measurement of superior peripheral vision) was assessed up to Day 14. Statistically significant, but numerically small, improvements vs. vehicle were noted. As a secondary endpoint, marginal reflex distance of the upper lid (MRD_1) was assessed up to Day 42. The relative improvement in MRD_1 was statistically significant favoring Upneeq over vehicle, but the treatment difference vs. vehicle was small (approximately 0.5 mm). Both pivotal trials were 6 weeks in duration; long-term efficacy beyond 6 weeks has not been evaluated.

Guidelines

Upneeq is not addressed in guidelines. The American Academy of Ophthalmology issued a report in 2011 detailing functional indications for upper eyelid ptosis and blepharoplasty surgery.[5] Ptosis and upper eyelid blepharoplasty surgery were found to be functionally beneficial under the following circumstances:

- $MRD_1 \leq 2$ mm measured in primary gaze; or
- Superior visual field loss of 12 degrees or 24%; or
- Down-gaze ptosis impairing reading documented by $MRD_1 \leq 2$ mm measured in down gaze; or
- Self-reported functional impairment from upper eyelid droop; or
- Chin-up backward head tilt induced by visual field impairment caused by lids; or
- Interference with occupational duties and safety resulting from visual impairment caused by the upper lids; or
- Symptoms of discomfort, eye strain, or visual interference due to upper eyelid position.

POLICY STATEMENT

Due to insufficient clinical efficacy data, **approval is not recommended** for Upneeq.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Upneeq is not recommended in the following situations:

222. Blepharoptosis. Due to insufficient clinical efficacy data, approval is not recommended for Upneeq.

223. Conjunctivitis. A lower strength of oxymetazoline solution (0.025%) has been evaluated for treatment of allergic and non-infectious conjunctivitis and was previously marketed over-the-counter under the name Visine® Long Lasting (no longer marketed). Oxymetazoline solution 0.1% has not been evaluated for conjunctivitis. Other over-the-counter alpha-adrenergic agonists are available as

eye drops, including Visine® (tetrahydrolozine hydrochloride 0.05%) and Naphcon-A® (naphazoline hydrochloride 0.025%).

224. Cosmetic uses. Coverage of Upneeq for cosmetic uses (i.e., blepharoptosis when functional limitation is absent) is not recommended as cosmetic uses are excluded from coverage in a typical pharmacy benefit.

225. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

697. Upneeq™ ophthalmic solution [prescribing information]. Bridgewater, NJ: Osmotica/RVL Pharmaceuticals; July 2020.
698. Shahzad B, Siccardi MA. Ptosis. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; updated January 1, 2020. Available at: https://www.ncbi.nlm.nih.gov/books/NBK546705/. Accessed on July 17, 2020.
699. Slonim C, Silverberg M, Butler B, et al. RVL-1201 ophthalmic solution improves the superior field of vision in subjects with upper eyelid ptosis. Presented at: 2017ARVO Annual Meeting; Baltimore, MD: May 7-11, 2017.
700. Data on file. Osmotica Pharmaceutical US, LLC; received July 2020.
701. Cahill KV, Bradley EA, Meyer DR, et al. Functional indications for upper eyelid ptosis and blepharoplasty surgery: a report by the American Academy of Ophthalmology. *Ophthalmology*. 2011;118(12):2510-2517.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/19/2020

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Beovu Prior Authorization Policy

- Beovu® (brolucizumab for intravitreal injection – Novartis)

REVIEW DATE: 11/04/2020

OVERVIEW

Beovu, a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the treatment of neovascular (wet) age-related macular degeneration.[1] The recommended dose for Beovu is 6 mg administered by intravitreal (IVT) injection every month (every 25 to 31 days) for the first 3 doses, followed by 6 mg IVT injection once every 8 to 12 weeks.

Other Uses with Supportive Evidence

Overproduction of VEGF may lead to other eye conditions, including neovascular glaucoma, retinopathy of prematurity, and other retinal and choroidal neovascular conditions affecting the eye, the VEGF inhibitors also have the potential to be used off-label and reduce vision loss associated with other eye conditions related to increased VEGF production.[2,3] The use of anti-VEGF agents have been shown to stop the angiogenic process and maintain visual acuity and improve vision in patients with certain neovascular ophthalmic conditions; therefore, research is rapidly evolving on the use of VEGF inhibitors in other neovascular ophthalmic conditions which threaten vision.[4,5] Anti-VEGF therapy has the potential to be used off-label in other neovascular conditions affecting the eye and may prevent or slow visual impairment.[2,4,5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Beovu. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with

Beovu as well as the monitoring required for adverse events and long-term efficacy, approval requires Beovu to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Beovu is recommended in those who meet the following criteria:

FDA-Approved Indications

235. Neovascular (Wet) Age-Related Macular Degeneration. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Other Uses with Supportive Evidence

236. Other Neovascular Diseases of the Eye (e.g., neovascular glaucoma, retinopathy of prematurity, sickle cell neovascularization, choroidal neovascular conditions, etc.). Approve for 1 year if administered by or under the supervision of an ophthalmologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Beovu is not recommended in the following situations:

226. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

702. Beovu® [prescribing information]. Hanover, NJ: Novartis Pharmaceuticals; June 2020.
703. Barakat MR, Kaiser PK. VEGF inhibitors for the treatment of neovascular age-related macular degeneration. *Expert Opin Investig Drugs*. 2009;18(5):637-646.
704. Tolentino M. Systemic and ocular safety of intravitreal anti-VEGF therapies for ocular neovascular disease. *Surv Ophthalmol*. 2011;56(2):95-113.
705. Kinnunen K, Ylä-Herttuala S. Vascular endothelial growth factors in retinal and choroidal neovascular diseases. *Ann Med*. 2012;44(1):1-17.
706. Horsley MB, Kahook MY. Anti-VEGF therapy for glaucoma. *Curr Opin Ophthalmol*. 2010;21(2):112-117.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/23/2019
Annual Revision	No criteria changes.	11/04/2020

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Eylea Prior Authorization Policy

- Eylea® (aflibercept for intravitreal injection – Regeneron)

REVIEW DATE: 11/04/2020

OVERVIEW

Eylea, a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the following uses:[1]

- **Diabetic macular edema**.
- **Diabetic retinopathy**.
- **Macular edema following retinal vein occlusion**.
- **Neovascular (wet) age-related macular degeneration**.

The recommended dose for Eylea is 2 mg administered by intravitreal injection. Frequency of the dose does vary depending on the condition, although all conditions state some patients may need upper limit dosing of once every 4 weeks (approximately every 25 days, monthly).

Other Uses with Supportive Evidence

Overproduction of VEGF may lead to other eye conditions, including neovascular glaucoma, retinopathy of prematurity, and other retinal and choroidal neovascular conditions affecting the eye, the VEGF inhibitors also have the potential to be used off-label and reduce vision loss associated with other eye conditions related to increased VEGF production.[2,3] The use of anti-VEGF agents have been shown to stop the angiogenic process and maintain visual acuity and improve vision in patients with certain neovascular ophthalmic conditions; therefore, research is rapidly evolving on the use of VEGF inhibitors in other neovascular ophthalmic conditions which threaten vision.[4,5] Anti-VEGF therapy has the potential to be used off-label in other neovascular conditions affecting the eye and may prevent or slow visual impairment.[2,4,5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Eylea. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Eylea as well as the monitoring required for adverse events and long-term efficacy, approval requires Eylea to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Eylea is recommended in those who meet the following criteria:

FDA-Approved Indications

237.Diabetic Macular Edema. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

238. Diabetic Retinopathy. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

239. Macular Edema Following Retinal Vein Occlusion. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

240. Neovascular (Wet) Age-Related Macular Degeneration. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Other Uses with Supportive Evidence

5. Other Neovascular Diseases of the Eye (e.g., neovascular glaucoma, retinopathy of prematurity, sickle cell neovascularization, choroidal neovascular conditions, etc.). Approve for 1 year if administered by or under the supervision of an ophthalmologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Eylea is not recommended in the following situations:

227. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

707. Eylea® injection [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; August 2019.
708. Barakat MR, Kaiser PK. VEGF inhibitors for the treatment of neovascular age-related macular degeneration. *Expert Opin Investig Drugs*. 2009;18(5):637-646.
709. Tolentino M. Systemic and ocular safety of intravitreal anti-VEGF therapies for ocular neovascular disease. *Surv Ophthalmol*. 2011;56(2):95-113.
710. Kinnunen K, Ylä-Herttuala S. Vascular endothelial growth factors in retinal and choroidal neovascular diseases. *Ann Med*. 2012;44(1):1-17.
711. Horsley MB, Kahook MY. Anti-VEGF therapy for glaucoma. *Curr Opin Ophthalmol*. 2010;21(2):112-117.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Updated duration of approvals to 1 year.	11/14/2018
Selected Revision	**Diabetic Retinopathy in patients with Diabetic Macular Edema**. This condition was update to include all patients with **Diabetic Retinopathy**. Previously the product was only indicated to treatment Diabetic Retinopathy in patients who also had Diabetic Macular Edema.	05/23/2019
Annual Revision	No criteria changes.	11/06/2019
Annual Revision	No criteria changes.	11/04/2020

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Lucentis Prior Authorization Policy

- Lucentis® (ranibizumab for intravitreal injection – Genentech)

REVIEW DATE: 11/04/2020

OVERVIEW

Lucentis, a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the following uses:[1]

- **Diabetic macular edema** (DME).
- **Diabetic retinopathy** (DR).
- **Macular edema following retinal vein occlusion** (RVO).
- **Myopic choroidal neovascularization** (mCNV).
- **Neovascular (wet) age-related macular degeneration** (AMD).

The recommended dose for Lucentis in DME and DR is 0.3 mg administered by intravitreal injection once every month (approximately 28 days). The recommended dose for Lucentis in wet AMD, macular edema following RVO, and mCNV is 0.5 mg administered by intravitreal injection once every month (approximately 28 days).

Other Uses with Supportive Evidence

Overproduction of VEGF may lead to other eye conditions, including neovascular glaucoma, retinopathy of prematurity, and other retinal and choroidal neovascular conditions affecting the eye, the VEGF inhibitors also have the potential to be used off-label and reduce vision loss associated with other eye conditions related to increased VEGF production.[2,3] The use of anti-VEGF agents have been shown to stop the angiogenic process and maintain visual acuity and improve vision in patients with certain neovascular ophthalmic conditions; therefore, research is rapidly evolving on the use of VEGF inhibitors in other neovascular ophthalmic conditions which threaten vision.[4,5] Anti-VEGF therapy has the potential to be used off-label in other neovascular conditions affecting the eye and may prevent or slow visual impairment.[2,4,5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lucentis. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lucentis as well as the monitoring required for adverse events and long-term efficacy, approval requires Lucentis to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lucentis is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Diabetic Macular Edema.** Approve for 1 year if administered by or under the supervision of an ophthalmologist.

2. **Diabetic Retinopathy.** Approve for 1 year if administered by or under the supervision of an ophthalmologist.

3. **Macular Edema Following Retinal Vein Occlusion.** Approve for 1 year if administered by or under the supervision of an ophthalmologist.

4. **Myopic Choroidal Neovascularization.** Approve for 1 year if administered by or under the supervision of an ophthalmologist.

5. **Neovascular (Wet) Age-Related Macular Degeneration.** Approve for 1 year if administered by or under the supervision of an ophthalmologist.

Other Uses with Supportive Evidence

6. **Other Neovascular Diseases of the Eye (e.g., neovascular glaucoma, retinopathy of prematurity, sickle cell neovascularization, choroidal neovascular conditions, etc.).** Approve for 1 year if administered by or under the supervision of an ophthalmologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lucentis is not recommended in the following situations:

228. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

712. Lucentis® intravitreal injection [prescribing information]. South San Francisco, CA: Genentech, Inc.; November 2019.
713. Barakat MR, Kaiser PK. VEGF inhibitors for the treatment of neovascular age-related macular degeneration. *Expert Opin Investig Drugs.* 2009;18(5):637-646.
714. Tolentino M. Systemic and ocular safety of intravitreal anti-VEGF therapies for ocular neovascular disease. *Surv Ophthalmol.* 2011;56(2):95-113.
715. Kinnunen K, Ylä-Herttuala S. Vascular endothelial growth factors in retinal and choroidal neovascular diseases. *Ann Med*. 2012;44(1):1-17.
716. Horsley MB, Kahook MY. Anti-VEGF therapy for glaucoma. *Curr Opin Ophthalmol*. 2010;21(2):112-117.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Updated duration of approvals to 1 year.	11/14/2018
Annual Revision	No criteria changes.	11/06/2019
Annual Revision	No criteria changes.	11/04/2020

PRIOR AUTHORIZATION POLICY

POLICY: Opioids – Fentanyl Transmucosal Drugs Prior Authorization Policy

- Abstral® (fentanyl sublingual tablet – Novartis/ProStrakan)
- Actiq® (oral transmucosal fentanyl citrate – Cephalon, generics)
- Fentora® (fentanyl buccal tablet – Cephalon, authorized generic)
- Lazanda® (fentanyl nasal spray – Depomed)
- Subsys® (fentanyl sublingual spray – Insys)

REVIEW DATE: 10/21/2020

OVERVIEW

The transmucosal fentanyl drugs are indicated only for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.[1-6]

Actiq (generics), Abstral, Fentora, and Subsys are immediate-release oral transmucosal formulations of fentanyl citrate.[1-5] Lazanda is a nasal spray intended for intranasal transmucosal administration.[6] Patients considered opioid tolerant are those who are taking at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg oral hydromorphone daily, at least 25 mg oral oxymorphone daily, or an equianalgesic dose of another opioid for a week or longer. The appropriate dosing and safety of Actiq (generics) in opioid tolerant children with breakthrough cancer pain have not been established in those below 16 years of age.[1,3] The safety and efficacy of Abstral, Fentora, Subsys, and Lazanda have not been established in pediatric patients below 18 years of age.[2,4-6]

The transmucosal fentanyl drugs are contraindicated in the management of acute or postoperative pain and in patients with known intolerance or hypersensitivity to any components or the drug fentanyl.[1-6] In addition, these products must not be used in opioid non-tolerant patients (contraindicated). The transmucosal fentanyl drugs are approved for use only in the care of cancer patients and only by healthcare professionals[1-5] (oncologists and pain specialists)[2,3,6] who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain. Because of the risk of misuse, abuse, addition, and overdose, these products are available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Transmucosal Immediate-Release Fentanyl (TIRF) REMS ACCESS program. Under the TIFR REMS ACCESS program, outpatients, prescribers who prescribe to outpatients, pharmacies, and distributors must enroll in the program.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of fentanyl transmucosal drugs. All approvals are provided for the duration noted below.

Automation: If the patient has a prescription for a cancer medication (see Appendix A) within a 180-day period, the claim will adjudicate. When available, the ICD-10 codes for cancer will be used as part of automation to allow approval of the requested medication (see Appendix B).

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of fentanyl transmucosal drugs is recommended for those who meet one of the following criteria:

FDA-Approved Indications

1. **Breakthrough Pain in Patients with Cancer.** Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient meets ONE of the following conditions (i or ii):
     - **i.** Patient is unable to swallow, has dysphagia, esophagitis, mucositis, or uncontrollable nausea/vomiting; OR
     - **ii.** Patient is unable to take two other short-acting narcotics secondary to allergy or severe adverse events; AND

Note: Examples of short-acting narcotics include immediate-release formulations of oxycodone, morphine sulfate, hydromorphone, etc.

B) Patient is on or will be on an oral or transdermal long-acting narcotic, or the patient is on intravenous, subcutaneous, or spinal (intrathecal, epidural) narcotics.
Note: Examples of long-acting narcotics include Duragesic, OxyContin, and morphine extended-release. Examples of intravenous, subcutaneous, or spinal narcotics include morphine sulfate, hydromorphone, and fentanyl citrate.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of fentanyl transmucosal drugs is not recommended in the following situations:

1. **Acute and/or Postoperative Pain.** This includes surgery/post-surgery, trauma/post-trauma, acute medical illness (acute abdominal pain, pelvic pain, muscle spasm), Actiq (generics), Abstral, Fentora, Lazanda, and Subsys are contraindicated for use in the management of acute or postoperative pain, including migraine headache pain.[1-6] A case series reported the efficacious outpatient use (75% reduction in pain intensity at 2 hours; n = 18) of Actiq for the management of treating an acute, refractory migraine headache in 20 patients.[7] Actiq was used as a rescue medication for management of a moderate to severe migraine after ineffective treatment with the patients' usual antimigraine therapy. All of these patients were managed by a headache clinic and had undergone a full evaluation of their medical history, vital signs, and physical and neurological examinations. In addition, all 20 patients had been previously treated with multiple other therapies (e.g., 5-hydroxytryptamine $[5\text{-HT}]_1$ receptor agonists, ergots, antiemetics, prescription and over-the-counter analgesics, and anti-inflammatory drugs) and all had previously received outpatient opioid therapies in an attempt to manage their migraine pain. All patients were also known responders to use of parenteral opioid therapy. Side effects reported included nausea (n = 3), vomiting (n = 1), somnolence (n = 2), itching (n = 1), and dry mouth (n = 1). Controlled research is needed to fully determine the role of Actiq for the management of acute, refractory migraine.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Actiq® oral transmucosal [prescribing information]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; October 2019.
2. Fentora® buccal tablet [prescribing information]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; October 2019.
3. Oral Transmucosal Fentanyl Citrate (OTFC) [prescribing information]. Chestnut Ridge, NY: Par Pharmaceuticals; March 2017.
4. Abstral® sublingual tablets [prescribing information]. Solana Beach, CA: Sentynl Therapeutics, Inc.; October 2019.
5. Subsys® sublingual spray [prescribing information]. Chandler, AZ: Insys Therapeutics, Inc.; October 2019.
6. Lazanda® nasal spray [prescribing information]. Northbrook, IL: West Therapeutic Development, LLC; October 2019.
7. Landy SH. Oral transmucosal fentanyl citrate for the treatment of migraine headache pain in outpatients: a case series. *Headache.* 2004;44(8):762-766.

HISTORY

Type of Revision	Summary of Changes	Review Date
Selected Revision	Removal of criteria for the "Other Use with Supportive Evidence" of Breakthrough Chronic (Non-Cancer) Pain. This decision was made to be consistent with the Opioid Management solution and supported by external guidance. Automation is being changed to only look back for cancer medications and/or ICD-9/ICD-10 codes for cancer/hospice.	01/24/2018
Selected Revision	Automation will only look back for cancer medications and/or ICD-9/ICD-10 codes for cancer (not hospice) in order to align the automation with criteria changes from 1/24/18.	02/07/2018

Annual Revision	Removal of Onsolis which has been off the market for > 3 years. Removal of Condition Not Recommended for Approval of pre-anesthesia.	10/3/2018
Annual Revision	No change to criteria.	10/23/2019
Annual Revision	**Breakthrough Pain in Patients with Cancer:** Removed the statement "In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion" from criteria. Changed examples of narcotics to notes. Four new STC codes were added to Appendix A, and the ICD-9 codes were removed from Appendix B because they are no longer used.	10/21/2020

APPENDIX A

Note: This list is not inclusive. As new STCs become available, they will roll into this policy and the list will be updated periodically.

STC*	STC Description
0470	ANTINEOPLASTIC - ALKYLATING AGENTS
0471	ANTINEOPLASTIC - ANTIMETABOLITES
0472	ANTINEOPLASTIC - VINCA ALKALOIDS
0473	ANTIBIOTIC ANTINEOPLASTICS
0475	ANTINEOPLASTICS, MISCELLANEOUS
6323	ANTINEOPLASTIC - ANTIANDROGENIC AGENTS
7235	ANTINEOPLASTICS ANTIBODY/ANTIBODY-DRUG COMPLEXES
7977	ANTINEOPLASTIC IMMUNOMODULATOR AGENTS
8254	ANTINEOPLASTIC LHRH(GNRH) AGONIST, PITUITARY SUPPR.
8460	ANTINEOPLASTIC LHRH(GNRH) ANTAGONIST,PITUIT.SUPPRS
8569	ANTINEOPLASTIC EGF RECEPTOR BLOCKER MCLON ANTIBODY
8585	ANTINEOPLAST HUM VEGF INHIBITOR RECOMB MC ANTIBODY
9150	ANTINEOPLASTIC SYSTEMIC ENZYME INHIBITORS
B759	ANTINEOPLAST, HISTONE DEACETYLASE (HDAC) INHIBITORS
C232	ANTINEOPLASTIC - MTOR KINASE INHIBITORS
C370	ANTINEOPLASTIC - EPOTHILONES AND ANALOGS
C532	ANTINEOPLASTIC - TOPOISOMERASE I INHIBITORS
C593	ANTINEOPLASTIC - AROMATASE INHIBITORS
D426	ANTINEOPLASTIC - IMMUNOTHERAPY, THERAPEUTIC VAC
D560	ANTINEOPLASTIC - HALICHONDRIN B ANALOGS
D687	CYTOTOXIC T-LYMPHOCYTE ANTIGEN (CTLA-4) RMC ANTIBODY
E039	ANTINEOPLASTIC - JANUS KINASE (JAK) INHIBITORS
E150	ANTINEOPLASTIC - HEDGEHOG PATHWAY INHIBITOR
E600	ANTINEOPLASTIC - VEGF-A,B AND PLGF INHIBITORS
F495	ANTINEOPLASTIC - INTERLEUKIN-6(IL-6)INHIB,ANTIBODY
F501	ANTINEOPLASTIC - VEGFR ANTAGONIST
F665	ANTINEOPLASTIC, ANTI-PROGRAMMED DEATH-1 (PD-1) MAB
G545	ANTINEOPLASTIC - IMMUNOTHERAPY, VIRUS-BASED AGENTS
G575	ANTINEOPLASTIC - MEK1 AND MEK2 KINASE INHIBITORS
G590	ANTINEOPLASTIC - ANTI-CD38 MONOCLONAL ANTIBODY
G607	ANTINEOPLASTIC - ANTI-SLAMF7 MONOCLONAL ANTIBODY
G802	ANTINEOPLASTIC- B CELL LYMPHOMA-2(BCL-2) INHIBITORS
G857	ANTI-PROGRAMMED CELL DEATH-LIGAND 1 (PD-L1) MAB
H018	ANTINEOPLASTIC, PDGFR-ALPHA BLOCKER MC ANTIBODY
H214	ANTINEOPLASTIC COMB-KINASE AND AROMATASE INHIBIT
H289	ANTINEOPLASTIC-ISOCITRATE DEHYDROGENASE INHIBITORS
H309	ANTINEOPLASTIC – ANTIBIOTIC AND ANTIMETABOLITE
H317	ANTINEOPLASTIC – CD22 ANTIBODY-CYTOTOXIC ANTIBIOTIC
H324	ANTINEOPLASTIC- CD19 DIR. CAR-T CELL IMMUNOTHERAPY
H329	ANTINEOPLASTIC – CD33 ANTIBODY-CYTOTOXIC ANTIBIOTIC
H617	ANTINEOPLASTIC – BRAF KINASE INHIBITORS
H768	ANTINEOPLASTIC-CD22 DIRECT ANTIBODY/CYTOTOXIN CONJ
H868	ANTINEOPLASTIC-CD123-DIRECTED CYTOTOXIN CONJUGATE
I054	ANTINEOPLASTIC-SELECT INHIB OF NUCLEAR EXP (SINE)
I264	ANTINEOPLASTIC – PROTEIN METHYLTRANSFERASE INHIBITORS

* Excluding topical products

APPENDIX B

ICD-10 Codes

Cancer-related codes
C00.* to D09.*
D3A.* to D48.*
E34.0*
Q85.0*

*Indicates the inclusion of subheadings.

PRIOR AUTHORIZATION POLICY

POLICY: Opioids – Long-Acting Products

Note: This is not an inclusive list. As new products become available, they will roll into this policy and the list will be updated periodically.

- Buprenorphine (i.e., Belbuca®, Butrans®)
- Fentanyl transdermal (Duragesic®, generics)
- Hydrocodone extended-release (e.g., Hysingla™ ER, Zohydro® ER)
- Hydromorphone extended-release (e.g., Exalgo® [brand discontinued 2019], generics)
- Methadone (e.g., Diskets®, Dolophine®, Methadose™, generics)
- Morphine sulfate extended-release (e.g., Arymo® ER, Embeda® [brand discontinued 2019], Kadian®, MS Contin®, generics)
- Oxycodone extended-release (e.g., Xtampza® ER, OxyContin®)
- Oxymorphone extended-release (e.g., generics [generics are not AB-rated to the discontinued Opana® ER formulation])
- Tapentadol extended-release (e.g., Nucynta® ER)
- Tramadol extended-release (e.g., Conzip®, Ultram® ER, generics)

DATE REVIEWED: 04/29/2020

OVERVIEW

Opioid analgesics are commonly used for the management of pain.[1] An estimated 20% of patients presenting to physician offices with pain symptoms or pain-related diagnoses (including acute and chronic pain) unrelated to cancer receive an opioid prescription.

The currently available long-acting (due to either an extended-release formulation or a long half-life [i.e., methadone]) opioids are buprenorphine, fentanyl, hydrocodone, hydromorphone, methadone, morphine sulfate, oxycodone, oxymorphone, tapentadol, and tramadol.[2-17] All of the long-acting opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Extended-release opioid dosage forms offer a long duration of effect, reduce severity of end-of-dose pain, and allow many patients to sleep through the night. OxyContin is the only product specifically indicated in pediatric patients 11 years to 18 years of age.[7] Nucynta ER is the only product also indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy in adults.[2]

These medications produce the majority of their effects by binding to μ, κ, and δ receptors in the central nervous system.[3-17] However, Nucynta ER and Ultram ER/Conzip have a unique dual mechanism of action.[2,14] They demonstrate μ-opioid agonist activity and inhibition of norephinephrine reuptake (and serotonin reuptake for tramadol). Methadone has additional indications for the treatment and maintenance treatment of opioid addiction (i.e., heroin or other morphine-like drugs).[17] Note that methadone products

when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority.

Since the 1990s, opioid use and abuse have risen markedly in the US.[18] An estimated 3.3 million people aged ≥ 12 years in 2016 were current misusers of pain relievers, which represents 1.2% of the population aged ≥ 12 years.[19] In 2016, an estimated 239,000 adolescents aged 12 years to 17 years (1%), 631,000 young adults aged 18 years to 25 years (1.8%), and 2.5 million adults aged ≥ 26 years (1.2%) were current misusers of pain relievers.

In 2016, the Centers for Disease Control (CDC) published a guideline for prescribing opioids for chronic pain.[1,20] The guideline provides recommendations for primary care providers who are prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. In the guideline, chronic pain is defined as pain that typically lasts greater than 3 months or past the time of normal tissue healing, resulting from an underlying medical disease or condition, injury, medical treatment, inflammation, or an unknown cause. To support the guideline an updated review of long-term opioid therapy for chronic pain outside of end-of-life care was undertaken and the results revealed that evidence remains limited, with insufficient evidence to determine long-term benefits of chronic opioid therapy versus no opioid therapy. However, the evidence did suggest a risk for serious harms with long-term opioid therapy that appears to be dose-dependent.

The CDC guideline recommendations are grouped into three areas: when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing risk and addressing harms of opioid use.[1] Nonpharmacologic therapy and non-opioid pharmacologic therapy are preferred for chronic pain; if opioids are used, they should be combined with nonpharmacologic therapy and non-opioid pharmacologic therapy, as appropriate. Before starting and periodically during opioid therapy, healthcare providers should discuss with their patient the risks and realistic benefits of opioid therapy and also the shared responsibilities for managing therapy. When starting opioid therapy for chronic pain, immediate-release opioids should be prescribed at the lowest effective dosage instead of initiating therapy with extended-release/long-acting opioids. Carefully reassess individual benefits and risks when increasing opioid dosages to ≥ 50 morphine milligram equivalents (MME)/day and avoid increasing dosage to ≥ 90 MME/day whenever possible. Healthcare providers should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy or of dose escalation and evaluate continued therapy with patients at least every 3 months. If benefits do not outweigh harms of continued opioid therapy, other therapies should be optimized and opioid doses tapered to lower dosages and/or discontinued. Before starting and periodically during continuation of opioid therapy, healthcare providers should evaluate risk factors for opioid-related harms and incorporate strategies into the management plan to mitigate risk, including offering naloxone. The patient's history of controlled substance prescriptions should be periodically reviewed using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations putting them at high risk for overdose. Urine drug testing is recommended before starting opioid therapy and at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs; treatment should be offered to and/or arranged for patients with opioid use disorder.

The CDC guideline states that long-term opioid use often begins with treatment of acute pain.[1] When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids (i.e., ≤ 3 days and only rarely > 7 days).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of long-acting opioids. Long-acting opioids are controlled substances (CII with the exception of tramadol-containing products which are CIV) which can be misused and abused. This policy includes long-acting formulations of the medications listed on page 1; the list is not inclusive. As new products become available, they will roll into this policy and the list will be updated periodically. All approvals are provided for 1 year in duration unless otherwise noted below.

Automation: Patients with a history of a long-acting opioid within the 130-day look-back period are excluded from prior authorization. If the patient has a prescription for a cancer medication (see Appendix A) within a 180-day period, the claim will adjudicate. When available, the ICD-10 codes for cancer will be used as part of automation to allow approval of the requested medication (see Appendix B).

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of long-acting opioids is recommended in those who meet the following criteria:

A. Coverage of all long-acting opioids, except fentanyl transdermal products, is recommended in those who meet the following criteria:

FDA-Approved Indications

27. Pain Severe Enough to Require Daily, Around-the-Clock, Long-Term Opioid Treatment. Approve for 1 year if the patient meets ONE of the following criteria (A, B or C):

- **A)** The patient has a cancer diagnosis; OR
- **B)** The patient is in a hospice program, end-of-life care, or palliative care; OR
- **C)** The patient has chronic pain but does not have a cancer diagnosis. Approve for 1 year if the patient meets ALL of the following criteria (i, ii, iii, iv, and v):
  - **i.** Patient is not opioid naïve; AND
  - **ii.** Non-opioid therapies (e.g., non-opioid medications [e.g., nonsteroidal anti-inflammatory drugs {NSAIDs}, tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors {SNRIs}, anticonvulsants], exercise therapy, weight loss, cognitive behavioral therapy) have been optimized and are being used in conjunction with opioid therapy according to the prescribing physician; AND
  - **iii.** The patient's history of controlled substance prescriptions has been checked using the state prescription drug monitoring program (PDMP), unless unavailable in the state (see note below), according to the prescribing physician; AND
  - **iv.** Risks (e.g., addiction, overdose) and realistic benefits of opioid therapy have been discussed with the patient according to the prescribing physician; AND
  - **v.** Treatment plan (including goals for pain and function) is in place and reassessments (including pain levels and function) are scheduled at regular intervals according to the prescribing physician.

Note: As of 04/24/2020, the state of Missouri is the only state in the US that does not have a statewide PDMP program in place.

2. Opioid Addiction (Dependence) [methadone products only]. Approve methadone for 1 year if ONE of the following criteria (A or B) is met:

- **A)** Methadone is dispensed by an opioid treatment program certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority; OR

B) Methadone is being prescribed during an emergency period of ≤ 3 days while definitive care for the addiction is being sought in an appropriately licensed facility.

B. Coverage of fentanyl transdermal products is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Pain Severe Enough to Require Daily, Around-the-Clock, Long-Term Opioid Treatment.** Approve for 1 year if the patient has a cancer diagnosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Long-acting opioids have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

289. **Acute pain.** According to the CDC guideline for prescribing opioids for chronic pain, clinicians should not prescribe extended-release/long-acting opioids for the treatment of acute pain due to the longer half-lives and longer duration of effects (e.g., respiratory depression) with extended-release/long-acting opioids.[1]

290. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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20. Embeda® extended-release capsules [prescribing information]. New York, NY: Pfizer Inc.; October 2019.
21. Kadian® capsules [prescribing information]. Madison, NJ: Allergan USA, Inc.; October 2019.
22. Avinza® capsules [prescribing information]. New York, NY: Pfizer Inc.; May 2014.
23. MS Contin® tablets [prescribing information]. Stamford, CT: Purdue Pharma L.P.; October 2019.
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26. Exalgo® extended-release tablets [prescribing information]. Webster Groves, MO: SpecGx LLC; October 2019.
27. Zohydro® ER extended-release capsules [prescribing information]. Morristown, NJ: Currax Pharmaceuticals LLC; October 2019.
28. Hysingla™ ER extended-release tablets [prescribing information]. Stamford, CT: Purdue Pharma L.P.; October 2019.
29. Xtampza ER® extended-release capsules [prescribing information]. Cincinnati, OH: Patheon Pharmaceuticals; October 2019.
30. Arymo® ER extended-release tablets [prescribing information]. Wayne, PA: Egalet US Inc.; October 2019.
31. Conzip® extended-release capsules [prescribing information]. Bridgewater, NJ: Vertical Pharmaceuticals, LLC; October 2019.
32. Belbuca® buccal film [prescribing information]. Raleigh, NC: BioDelivery Sciences International, Inc.; October 2019.
33. Duragesic® transdermal system [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; October 2019.
34. Dolophine® [prescribing information]. Eatontown, NJ: West-Ward Pharmaceuticals Corp.; October 2019.
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37. Centers for Disease Control and Prevention. Checklist for prescribing opioids for chronic pain. Available at: https://www.cdc.gov/drugoverdose/pdf/pdo_checklist-a.pdf. Accessed on April 24, 2020.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Selected revision	Removing criterion requiring a concurrent prescription for a short-acting opioid. The intent of this criterion was to assure that new users to LA opioid therapy had been initiated on therapy with a short-acting opioid; however, some long-term users of LA opioids are also being reviewed through PA. Fentanyl transdermal products were separated out and will be approved only for use in cancer patients or in patients in a hospice program, end-of-life care, or palliative care. The Automation section was updated to reflect existing automation, "Patients with a history of a long-acting opioid within the 130-day look-back period are excluded from prior authorization."	01/24/2018
Selected revision	Approval criterion for fentanyl transdermal products was changed to approve only for patients with cancer. Automation for this policy will only look back for cancer medications and/or ICD-9/ICD-10 codes for cancer.	02/07/2018
Annual revision	No changes to criteria.	03/21/2018
DEU revision	05/02/2018: Modification of the list of drugs included in this policy and addition of a statement in the Policy Statement indicating that this policy includes long-acting formulations of the medications listed on page 1; the list is not inclusive. As new products become available, they will roll into this policy and the list will be updated periodically. Similarly, the list in Appendix A is not inclusive.	--
Annual revision	STC code H868 was added to Appendix A. No change to criteria.	04/10/2019
Annual revision	No changes to criteria. Four new STC codes were added to Appendix A, and the ICD-9 codes were removed from Appendix B because they are no longer used.	04/29/2020

APPENDIX A

Note: This list is not inclusive. As new STCs become available, they will roll into this policy and the list will be updated periodically.

STC*	STC Description
0470	ANTINEOPLASTIC - ALKYLATING AGENTS
0471	ANTINEOPLASTIC - ANTIMETABOLITES
0472	ANTINEOPLASTIC - VINCA ALKALOIDS
0473	ANTIBIOTIC ANTINEOPLASTICS
0475	ANTINEOPLASTICS, MISCELLANEOUS
6323	ANTINEOPLASTIC - ANTIANDROGENIC AGENTS
7235	ANTINEOPLASTICS ANTIBODY/ANTIBODY-DRUG COMPLEXES
7977	ANTINEOPLASTIC IMMUNOMODULATOR AGENTS
8254	ANTINEOPLASTIC LHRH(GNRH) AGONIST, PITUITARY SUPPR.
8460	ANTINEOPLASTIC LHRH(GNRH) ANTAGONIST,PITUIT.SUPPRS
8569	ANTINEOPLASTIC EGF RECEPTOR BLOCKER MCLON ANTIBODY
8585	ANTINEOPLAST HUM VEGF INHIBITOR RECOMB MC ANTIBODY
9150	ANTINEOPLASTIC SYSTEMIC ENZYME INHIBITORS
B759	ANTINEOPLAST, HISTONE DEACETYLASE (HDAC) INHIBITORS
C232	ANTINEOPLASTIC - MTOR KINASE INHIBITORS
C370	ANTINEOPLASTIC - EPOTHILONES AND ANALOGS
C532	ANTINEOPLASTIC - TOPOISOMERASE I INHIBITORS
C593	ANTINEOPLASTIC - AROMATASE INHIBITORS
D426	ANTINEOPLASTIC - IMMUNOTHERAPY, THERAPEUTIC VAC
D560	ANTINEOPLASTIC - HALICHONDRIN B ANALOGS
D687	CYTOTOXIC T-LYMPHOCYTE ANTIGEN (CTLA-4) RMC ANTIBODY
E039	ANTINEOPLASTIC - JANUS KINASE (JAK) INHIBITORS
E150	ANTINEOPLASTIC - HEDGEHOG PATHWAY INHIBITOR
E600	ANTINEOPLASTIC - VEGF-A,B AND PLGF INHIBITORS
F495	ANTINEOPLASTIC - INTERLEUKIN-6(IL-6)INHIB,ANTIBODY
F501	ANTINEOPLASTIC - VEGFR ANTAGONIST
F665	ANTINEOPLASTIC, ANTI-PROGRAMMED DEATH-1 (PD-1) MAB
G545	ANTINEOPLASTIC - IMMUNOTHERAPY, VIRUS-BASED AGENTS
G575	ANTINEOPLASTIC - MEK1 AND MEK2 KINASE INHIBITORS
G590	ANTINEOPLASTIC - ANTI-CD38 MONOCLONAL ANTIBODY
G607	ANTINEOPLASTIC - ANTI-SLAMF7 MONOCLONAL ANTIBODY
G802	ANTINEOPLASTIC- B CELL LYMPHOMA-2(BCL-2) INHIBITORS
G857	ANTI-PROGRAMMED CELL DEATH-LIGAND 1 (PD-L1) MAB
H018	ANTINEOPLASTIC, PDGFR-ALPHA BLOCKER MC ANTIBODY
H214	ANTINEOPLASTIC COMB-KINASE AND AROMATASE INHIBIT
H289	ANTINEOPLASTIC-ISOCITRATE DEHYDROGENASE INHIBITORS
H309	ANTINEOPLASTIC – ANTIBIOTIC AND ANTIMETABOLITE
H317	ANTINEOPLASTIC – CD22 ANTIBODY-CYTOTOXIC ANTIBIOTIC
H324	ANTINEOPLASTIC- CD19 DIR. CAR-T CELL IMMUNOTHERAPY
H329	ANTINEOPLASTIC – CD33 ANTIBODY-CYTOTOXIC ANTIBIOTIC
H617	ANTINEOPLASTIC – BRAF KINASE INHIBITORS
H768	ANTINEOPLASTIC-CD22 DIRECT ANTIBODY/CYTOTOXIN CONJ
H868	ANTINEOPLASTIC-CD123-DIRECTED CYTOTOXIN CONJUGATE
I054	ANTINEOPLASTIC-SELECT INHIB OF NUCLEAR EXP (SINE)
I264	ANTINEOPLASTIC – PROTEIN METHYLTRANSFERASE INHIBITORS

* Excluding topical products

APPENDIX B

ICD-10 Codes
Cancer-related codes
C00.* to D09.*
D3A.* to D48.*
E34.0*
Q85.0*

*Indicates the inclusion of subheadings.

PRIOR AUTHORIZATION POLICY

POLICY: Opioids – Tramadol Extended-Release Prior Authorization Policy

- ConZip® (tramadol hydrochloride extended-release capsules – Vertical)
- Tramadol extended-release capsules – various (brand products)
- Tramadol hydrochloride extended-release tablets – generics to the discontinued product Ultram® ER
- Tramadol hydrochloride extended-release tablets – generics to the discontinued product Ryzolt

REVIEW DATE: 08/19/2020

OVERVIEW

Tramadol extended-release tablets, tramadol extended-release capsules, and ConZip are indicated for the management of pain severe enough to require daily around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.[1-3]

Tramadol is a centrally acting synthetic opioid analgesic.[1-3] The extended-release tramadol products differ in their extended-release mechanism. ConZip contains a total dose of tramadol in a combination of immediate-release and extended-release components. However, ConZip is bioequivalent to a reference extended-release tramadol product under fasting conditions. Therefore, clinical efficacy was based on a reference extended-release tramadol product.

Guidelines

In 2016, the Centers for Disease Control (CDC) published a guideline for prescribing opioids for chronic pain.[4,5] The guideline provides recommendations for primary care providers who are prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. In the guideline, chronic pain is defined as pain that typically lasts greater than 3 months or past the time of normal tissue healing, resulting from an underlying medical disease or condition, injury, medical treatment, inflammation, or an unknown cause. To support the guideline an updated review of long-term opioid therapy for chronic pain outside of end-of-life care was undertaken and the results revealed that evidence remains limited, with insufficient evidence to determine long-term benefits of chronic opioid therapy versus no opioid therapy. However, the evidence did suggest a risk for serious harms with long-term opioid therapy that appears to be dose-dependent.

The CDC guidelines recommend non-pharmacologic therapy and non-opioid pharmacologic therapy for chronic pain; if opioids are used, they should be combined with non-pharmacologic therapy and non-opioid pharmacologic therapy, as appropriate.[4] Before starting and periodically during opioid therapy, healthcare providers should discuss with their patient the risks and realistic benefits of opioid therapy and also the shared responsibilities for managing therapy. When starting opioid therapy for chronic pain, immediate-release opioids should be prescribed at the lowest effective dosage instead of initiating therapy with extended-release/long-acting opioids. Before starting and periodically during continuation of opioid therapy, healthcare providers should evaluate risk factors for opioid-related harms and incorporate

strategies into the management plan to mitigate risk, including offering naloxone. The patient's history of controlled substance prescriptions should be periodically reviewed using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations putting them at high risk for overdose. Urine drug testing is recommended before starting opioid therapy and at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs; treatment should be offered to and/or arranged for patients with opioid use disorder.

The CDC guideline states that long-term opioid use often begins with treatment of acute pain.[4] When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids, i.e., ≤ 3 days and only rarely > 7 days.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of tramadol extended-release products. Tramadol extended-release products are controlled substances (C-IV) which can be misused and abused. Additionally, due to the availability of generic tramadol extended-release tablets, approval of a branded tramadol extended-release product requires a previous trial of the generic. All approvals are provided for the duration noted below.

Automation: If a generic tramadol extended-release product is requested and the patient has history of a generic tramadol extended-release product within the 130-day look-back period, a prescription for a cancer medication (see Appendix A) within a 180-day period, or an ICD-10 code for cancer (see Appendix B), the claim will adjudicate.

RECOMMENDED CRITERIA

Coverage of a tramadol extended-release product is recommended in those who meet the following criteria:

FDA-Approved Indications

28. Pain Severe Enough to Require Daily, Around-the-Clock, Long-Term Opioid Treatment. Approve for 1 year if the patient meets ONE of the following criteria (A, B or C) AND D:

- **D)** Patient has a cancer diagnosis; OR
- **E)** Patient is in hospice program, end-of-life care, or palliative care; OR
- **F)** Patient has chronic pain but does not have a cancer diagnosis. Approve for 1 year if the patient meets ALL of the following criteria (i, ii, iii, iv, and v):
  - **vi.** Patient is not opioid naïve; AND
  - **vii.** Non-opioid therapies have been optimized and are being used in conjunction with opioid therapy according to the prescriber; AND
    Note: Examples of non-opioid therapies include non-opioid medications (e.g., nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, anticonvulsants), exercise therapy, weight loss, and cognitive behavioral therapy.
  - **viii.** Patient's history of controlled substance prescriptions has been checked using the state prescription drug monitoring program (PDMP), unless unavailable in the state (see note below), according to the prescriber; AND
    Note: As of 08/19/2020, the state of Missouri is the only state in the US that does not have a statewide PDMP program in place.
  - **ix.** Risks (e.g., addiction, overdose) and realistic benefits of opioid therapy have been discussed with the patient according to the prescriber; AND

x. Treatment plan (including goals for pain and function) is in place and reassessments (including pain levels and function) are scheduled at regular intervals according to the prescriber.

G) If a branded tramadol extended-release product is requested, the patient has tried generic tramadol extended-release tablets.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of a tramadol extended-release product is not recommended in the following situations:

291. Acute pain. According to the CDC guideline for prescribing opioids for chronic pain, clinicians should not prescribe extended-release/long-acting opioids for the treatment of acute pain due to the longer half-lives and longer duration of effects (e.g., respiratory depression) with extended-release/long-acting opioids.[4]

292. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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4. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR Recommendations and Reports. 2016;65(1):1-49.
5. Centers for Disease Control and Prevention. Checklist for prescribing opioids for chronic pain. Available at: https://www.cdc.gov/drugoverdose/pdf/pdo_checklist-a.pdf. Accessed on August 17, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Selected Revision	The Automation section was updated to reflect existing automation, "Patients with a history of a generic tramadol ER product within the 130-day look-back period are excluded from prior authorization." Hospice ICD-9/ICD-10 codes removed from Automation to be consistent with the Long-Acting Opioids PA policy. Removed the criterion requiring a concomitant prescription for a short-acting opioid.	02/07/2018
Update	2/21/2018: Clarification to Automation that the use of a history of a generic tramadol extended-release product, cancer medications, or ICD-9/ICD-10 codes for cancer is only for patients prescribed a generic tramadol extended-release product.	--
Annual Revision	No change to criteria.	08/01/2018
Annual Revision	No change to criteria. Removed the obsolete branded Ultram ER product from the policy. In the approval condition "Pain Severe Enough to Require Daily, Around-the-Clock, Long-Term Opioid Treatment", the date of the Note was updated.	08/07/2019
Annual Revision	No change to criteria. Four new STC codes were added to Appendix A, and the ICD-9 codes were removed from Appendix B because they are no longer used. For the approval condition of Pain Severe Enough to Require Daily, Around-the-Clock, Long-Term Opioid Treatment, examples of non-opioid therapies were moved to a note.	08/19/2020

APPENDIX A

Note: This list is not inclusive. As new STCs become available, they will roll into this policy and the list will be updated periodically.

STC*	STC Description
0470	ANTINEOPLASTIC - ALKYLATING AGENTS
0471	ANTINEOPLASTIC - ANTIMETABOLITES
0472	ANTINEOPLASTIC - VINCA ALKALOIDS
0473	ANTIBIOTIC ANTINEOPLASTICS
0475	ANTINEOPLASTICS, MISCELLANEOUS
6323	ANTINEOPLASTIC - ANTIANDROGENIC AGENTS
7235	ANTINEOPLASTICS ANTIBODY/ANTIBODY-DRUG COMPLEXES
7977	ANTINEOPLASTIC IMMUNOMODULATOR AGENTS
8254	ANTINEOPLASTIC LHRH(GNRH) AGONIST, PITUITARY SUPPR.
8460	ANTINEOPLASTIC LHRH(GNRH) ANTAGONIST,PITUIT.SUPPRS
8569	ANTINEOPLASTIC EGF RECEPTOR BLOCKER MCLON ANTIBODY
8585	ANTINEOPLAST HUM VEGF INHIBITOR RECOMB MC ANTIBODY
9150	ANTINEOPLASTIC SYSTEMIC ENZYME INHIBITORS
B759	ANTINEOPLAST, HISTONE DEACETYLASE (HDAC) INHIBITORS
C232	ANTINEOPLASTIC - MTOR KINASE INHIBITORS
C370	ANTINEOPLASTIC - EPOTHILONES AND ANALOGS
C532	ANTINEOPLASTIC - TOPOISOMERASE I INHIBITORS
C593	ANTINEOPLASTIC - AROMATASE INHIBITORS
D426	ANTINEOPLASTIC - IMMUNOTHERAPY, THERAPEUTIC VAC
D560	ANTINEOPLASTIC - HALICHONDRIN B ANALOGS
D687	CYTOTOXIC T-LYMPHOCYTE ANTIGEN (CTLA-4) RMC ANTIBODY
E039	ANTINEOPLASTIC - JANUS KINASE (JAK) INHIBITORS
E150	ANTINEOPLASTIC - HEDGEHOG PATHWAY INHIBITOR
E600	ANTINEOPLASTIC - VEGF-A,B AND PLGF INHIBITORS
F495	ANTINEOPLASTIC - INTERLEUKIN-6(IL-6)INHIB,ANTIBODY
F501	ANTINEOPLASTIC - VEGFR ANTAGONIST
F665	ANTINEOPLASTIC, ANTI-PROGRAMMED DEATH-1 (PD-1) MAB
G545	ANTINEOPLASTIC - IMMUNOTHERAPY, VIRUS-BASED AGENTS
G575	ANTINEOPLASTIC - MEK1 AND MEK2 KINASE INHIBITORS
G590	ANTINEOPLASTIC - ANTI-CD38 MONOCLONAL ANTIBODY
G607	ANTINEOPLASTIC - ANTI-SLAMF7 MONOCLONAL ANTIBODY
G802	ANTINEOPLASTIC- B CELL LYMPHOMA-2(BCL-2) INHIBITORS
G857	ANTI-PROGRAMMED CELL DEATH-LIGAND 1 (PD-L1) MAB
H018	ANTINEOPLASTIC, PDGFR-ALPHA BLOCKER MC ANTIBODY
H214	ANTINEOPLASTIC COMB-KINASE AND AROMATASE INHIBIT
H289	ANTINEOPLASTIC-ISOCITRATE DEHYDROGENASE INHIBITORS
H309	ANTINEOPLASTIC – ANTIBIOTIC AND ANTIMETABOLITE
H317	ANTINEOPLASTIC – CD22 ANTIBODY-CYTOTOXIC ANTIBIOTIC
H324	ANTINEOPLASTIC- CD19 DIR. CAR-T CELL IMMUNOTHERAPY
H329	ANTINEOPLASTIC – CD33 ANTIBODY-CYTOTOXIC ANTIBIOTIC
H617	ANTINEOPLASTIC – BRAF KINASE INHIBITORS
H768	ANTINEOPLASTIC-CD22 DIRECT ANTIBODY/CYTOTOXIN CONJ
H868	ANTINEOPLASTIC-CD123-DIRECTED CYTOTOXIN CONJUGATE
I054	ANTINEOPLASTIC-SELECT INHIB OF NUCLEAR EXP (SINE)
I264	ANTINEOPLASTIC – PROTEIN METHYLTRANSFERASE INHIBITORS

* Excluding topical products

APPENDIX B

ICD-10 Codes

Cancer-related codes
C00.* to D09.*
D3A.* to D48.*
E34.0*
Q85.0*

*Indicates the inclusion of subheadings.

PRIOR AUTHORIZATION POLICY

POLICY: Parkinson's Disease – Amantadine Extended-Release Drugs Prior Authorization with Step Therapy Policy
- Gocovri™ (amantadine extended-release capsules – Adamas Pharma)
- Osmolex ER™ (amantadine extended-release tablets – Vertical Pharmaceuticals)

REVIEW DATE: 12/16/2020; selected revision 02/10/2021

OVERVIEW

Gocovri, an extended-release capsule formulation of amantadine, is indicated for **patients with Parkinson's disease** the following uses:[1]
- **Dyskinesia**, in patients receiving levodopa-based therapy, with or without concomitant dopaminergic medications.
- **"Off" episodes**, as adjunctive treatment to levodopa/carbidopa.

Osmolex ER, an extended-release tablet formulation of amantadine, is indicated for the following uses:[2]
- **Drug-induced extrapyramidal reactions**, in adult patients.
- **Parkinson's disease**, in adult patients.

Amantadine hydrochloride is available as immediate-release capsules, tablets, and oral solution.[3-5] The amantadine immediate-release products are indicated for the prophylaxis and treatment of signs and symptoms of infection caused by various strains of influenza A virus; idiopathic Parkinson's disease [Paralysis Agitans], post-encephalitic parkinsonism, symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication, and in those elderly patients believed to develop parkinsonism in association with cerebral arteriosclerosis; and drug-induced extrapyramidal reactions.

Guidelines

The International Parkinson and Movement Disorder Society published an evidence-based review for treatment for motor symptoms of Parkinson's disease (2018). Amantadine is addressed, however specific formulations are not. The review categorically divides treatment recommendations by Parkinson's disease characteristics. Amantadine was noted to be likely efficacious and possibly useful in treatment for symptomatic monotherapy and symptomatic adjunct therapy in early or stable Parkinson's disease. For treatment of dyskinesia, amantadine was identified to be efficacious and clinically useful.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of amantadine extended-release products. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with amantadine extended-release products as well as the monitoring required for adverse events and long-term efficacy, approval requires amantadine extended-release products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Gocovri is recommended in those who meet the following criteria:

FDA-Approved Indications

~~74.~~71. **Parkinson's Disease.** Approve if patient meets ONE of the following (A or B):
- **A)** Initial Therapy. Approve for 3 months if the patient meets the following criteria (i, ii, iii , and iv):
  - **i.** Patient meets ONE of the following criteria (a or b):
    - **a)** Patient is experiencing dyskinesia; OR
    - **b)** Patient is experiencing "off" episodes; AND
      Note: Examples of "off" episodes include muscle stiffness, slow movements, or difficulty starting movements.
  - **ii.** Patient is currently receiving levodopa-based therapy (e.g., carbidopa/levodopa); AND
  - **iii.** Patient has tried immediate-release amantadine capsules, tablets, or oral solution and meets ONE of the following criteria (a or b):
    - **a)** Patient derived benefit from immediate-release amantadine but had intolerable adverse events, as determined by the prescriber; OR
    - **b)** Patient could not achieve a high enough dosage to gain adequate benefit, as determined by the prescriber; AND
  - **iv.** The medication is prescribed by or in consultation with a neurologist.
- **B)** Patients is Currently Receiving Gocovri. Approve for 1 year if the patient meets the following criteria (i, ii, iii, and iv):
  - **i.** Patient is currently receiving levodopa-based therapy (e.g., carbidopa/levodopa); AND
  - **ii.** Patient has tried immediate-release amantadine capsules, tablets, or oral solution and meets ONE of the following criteria (a or b):
    - **a)** Patient derived benefit from immediate-release amantadine but had intolerable adverse events, as determined by the prescriber; OR
    - **b)** Patient could not achieve a high enough dosage to gain adequate benefit, as determined by the prescriber; AND
  - **iii.** Patient has had a response to therapy (e.g., decrease in dyskinesia, decrease in "off" episodes), as determined by the prescriber; AND
    Note: Examples of "off" episodes include muscle stiffness, slow movements, or difficulty starting movements.
  - **iv.** The medication is prescribed by or in consultation with a neurologist.

II. Coverage of Osmolex ER is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Drug-Induced Extrapyramidal Reactions.** Approve if patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets the following criteria (i and ii):
     - **i.** Patient has tried immediate-release amantadine capsules, tablets, or oral solution and meets ONE of the following criteria (a or b):
       - **a)** Patient derived benefit from immediate-release amantadine but had intolerable adverse events, as determined by the prescriber; OR
       - **b)** Patient could not achieve a high enough dosage to gain adequate benefit, as determined by the prescriber; AND
     - **ii.** The medication is prescribed by or in consultation with a neurologist.
   - **B)** Patient is Currently Receiving Osmolex ER. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient has tried immediate-release amantadine capsules, tablets, or oral solution and meets ONE of the following criteria (a or b):

a) Patient derived benefit from immediate-release amantadine but had intolerable adverse events, as determined by the prescriber; OR
b) Patient could not achieve a high enough dosage to gain adequate benefit, as determined by the prescriber; AND

ii. Patient has had a response to therapy (e.g., decrease in extrapyramidal reactions), as determined by the prescriber; AND
iii. The medication is prescribed by or in consultation with a neurologist.

2. Parkinson's Disease. Approve if patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 3 months if the patient meets the following criteria (i and ii):
i. Patient has tried immediate-release amantadine capsules, tablets, or oral solution and meets ONE of the following criteria (a or b):
a) Patient derived benefit from immediate-release amantadine but had intolerable adverse events, as determined by the prescriber; OR
b) Patient could not achieve a high enough dosage to gain adequate benefit, as determined by the prescriber; AND
ii. The medication is prescribed by or in consultation with a neurologist.
B) Patient is Currently Receiving Osmolex ER. Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
i. Patient has tried immediate-release amantadine capsules, tablets, or oral solution and meets ONE of the following criteria (a or b):
a) Patient derived benefit from immediate-release amantadine but had intolerable adverse events, as determined by the prescriber; OR
b) Patient could not achieve a high enough dosage to gain adequate benefit, as determined by the prescriber; AND
ii. Patient has had a response to therapy (e.g., decrease in dyskinesia), as determined by the prescriber; AND
iii. The medication is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of amantadine extended-release products is not recommended in the following situations:

229. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

717. Gocovri™ extended-release capsules [prescribing information]. Emeryville, CA: Adamas Pharma LLC; February 2021.
718. Osmolex ER™ extended-release tablets [prescribing information]. Bridgewater, NJ: Vertical Pharmaceuticals, LLC.; October 2019.
719. Amantadine capsules [prescribing information]. Bridgewater, NJ: Alembic Pharmaceuticals, Inc.; July 2019.
720. Amantadine tablets [prescribing information]. Sunrise, FL: Cipla USA, Inc.; August 2019.
721. Amantadine oral solution [prescribing information]. Amityville, NY: Hi-Tech Pharmacal Co., Inc.; October 2020.
722. Fox SH, Katzenschlager R, Lim SY, et al. International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease. *Mov Disord*. 2018;33(8):1248-1266.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	12/19/2018
Update	1/16/2019: Addition of "Parkinson's Disease" to the title of the policy.	NA
Annual Revision	No criteria changes.	12/18/2019
Annual Revision	No criteria changes.	12/16/2020
Selected Revision	**Dyskinesia in Parkinson's Disease:** For Gocovri, the indication was changed to **Parkinson's Disease**. Dyskinesia, along with the new indication for "off" episodes were added to criteria for approval.	02/10/2021

PRIOR AUTHORIZATION POLICY

POLICY: Parkinson's Disease – Apokyn Prior Authorization Policy

- Apokyn® (apomorphine hydrochloride for subcutaneous injection)

REVIEW DATE: 08/19/2020; selected revision 10/21/2020

OVERVIEW

Apokyn, a non-ergoline dopamine agonist, is indicated for the acute, intermittent treatment of hypomobility, "off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) associated with advanced Parkinson's disease.[1]

Guidelines

The American Academy of Neurology published guidelines in 2006 on the treatment of Parkinson's disease with motor fluctuations and dyskinesia.[2] The guidelines are dated and do not include more recently approved medications. It is recommended to offer entacapone and rasagiline to reduce "off" time (Level A). Pergolide (withdrawn from the market in 2007 due to risk of valvular fibrosis), pramipexole, ropinirole, and tolcapone (used with caution; requires monitoring for hepatotoxicity) should be considered to reduce "off" time (Level B). Apokyn® (apomorphine hydrochloride injection), cabergoline, and selegiline may be used to reduce "off" time (Level C). According to the guidelines, the available evidence does not establish superiority of one medication over another in reducing "off" time (Level B). Sustained-release levodopa/carbidopa and bromocriptine should not be considered to reduce "off" time (Level C). Amantadine may be used to reduce dyskinesia (Level C).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Apokyn. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Apokyn as well as the monitoring required for adverse events and long-term efficacy, approval requires Apokyn to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Apokyn is recommended in those who meet the following criteria:

FDA-Approved Indications

29. Parkinson's Disease. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):

- **i.** Patient is experiencing "off" episodes such as muscle stiffness, slow movements, or difficulty starting movements; AND
- **ii.** Patient is currently receiving carbidopa/levodopa therapy; AND

iii. Patient has previously tried one other treatment for "off" episodes and meets ONE of the following criteria (i or ii):

a) Patient had significant intolerance, according to the prescriber; OR

b) Patient had inadequate efficacy, according to the prescriber; AND

Note: Examples of treatment for "off" episodes include entacapone, rasagiline, pramipexole, ropinirole, tolcapone, cabergoline, selegiline, Kynmobi™ (apomorphine hydrochloride sublingual film), Ongentys® (opicapone capsules), or Xadago® (safinamide tablets).

D) Apokyn is being prescribed by, or in consultation with, a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Apokyn is not recommended in the following situations:

230. Concurrent Use with a Serotonin 5-HT3 Antagonist. Administration of Apokyn in conjunction with a serotonin 5-HT3 antagonist (e.g., ondansetron, granisetron, dolasetron, palonosetron, alosetron) can result in extreme lowering of blood pressure and loss of consciousness and is considered an absolute contraindication.[1]

231. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

723. Apokyn® subcutaneous injection [prescribing information] Louisville, KY: US WorldMeds; April 2020.

724. Pahwa R, Factor SA, Lyons KE, et al. Practice parameter: Treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review). Report of the quality standards subcommittee of the American Academy of Neurology. Neurology. 2006;66:983-995.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/28/2019
Annual Revision	**Parkinson's Disease.** For the requirement of previously tried treatments, the number of medications was changed from two treatments to one and criteria for significant intolerance and inadequate efficacy for those treatments was added. Kynmobi and Ongentys were added to the Note of previously tried Parkinson's disease treatments.	08/19/2020
Selected Revision	**Parkinson's Disease.** The requirement for the patient to have advanced Parkinson's disease was removed from criteria.	10/21/2020

PRIOR AUTHORIZATION POLICY

POLICY: Parkinson's Disease – Duopa Prior Authorization Policy

- Duopa™ (carbidopa and levodopa enteral suspension – AbbVie)

REVIEW DATE: 08/19/2020

OVERVIEW

Duopa, a combination of carbidopa (an aromatic amino acid decarboxylation inhibitor) and levodopa (an aromatic amino acid), is indicated for the treatment of motor fluctuations in patients with advanced Parkinson's disease.[1] Duopa is administered over a 16 hours/day infusion period through a naso-jejunal tube (short-term administration) or a percutaneous endoscopic gastrostomy-jejunostomy (long-term administration) using a CADD-Legacy® 1400 pump.

Guidelines

The American Academy of Neurology published guidelines in 2006 on the treatment of Parkinson's disease with motor fluctuations and dyskinesia.[2] The guidelines are dated and do not include more recently approved medications. It is recommended to offer entacapone and rasagiline to reduce "off" time (Level A). Pergolide (withdrawn from the market in 2007 due to risk of valvular fibrosis), pramipexole, ropinirole, and tolcapone (used with caution; requires monitoring for hepatotoxicity) should be considered to reduce "off" time (Level B). Apokyn® (apomorphine hydrochloride injection), cabergoline, and selegiline may be used to reduce "off" time (Level C). According to the guidelines, the available evidence does not establish superiority of one medication over another in reducing "off" time (Level B). Sustained-release levodopa/carbidopa and bromocriptine should not be considered to reduce "off" time (Level C). Amantadine may be used to reduce dyskinesia (Level C).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Duopa. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Duopa as well as the monitoring required for adverse events and long-term efficacy, approval requires Duopa to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Duopa is recommended in those who meet the following criteria:
FDA-Approved Indications

241. Parkinson's Disease. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):

- **A)** Patient is diagnosed with advanced Parkinson's disease; AND
- **B)** Patient is experiencing "off" episodes such as muscle stiffness, slow movements, or difficulty starting movements; AND
- **C)** Patient has tried an oral extended-release carbidopa/levodopa therapy and meets one of the following criteria (i or ii):
  - **i.** Patient had significant intolerance, according to the prescriber; OR
  - **ii.** Patient had inadequate efficacy, according to the prescriber; AND
- **D)** Patient has previously tried three other treatments for "off" episodes; AND
  Note: Examples of treatment for "off" episodes include entacapone, rasagiline, pramipexole, ropinirole, tolcapone, cabergoline, selegiline, Kynmobi™ (apomorphine hydrochloride sublingual film), Ongentys® (opicapone capsules), or Xadago® (safinamide tablets).
- **E)** Duopa is being prescribed by, or in consultation with, a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Duopa is not recommended in the following situations:

232. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

725. Duopa™ [prescribing information] Bridgewater, NJ: Valeant Pharmaceuticals; May 2020.

726. Olanow CW, Kieburtz KK, Espay AJ, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomized, controlled, double-blind, double-dummy study. *Lancet Neurol*. 2014;13:141-149.
727. Pahwa R, Factor SA, Lyons KE, et al. Practice parameter: Treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review). Report of the quality standards subcommittee of the American Academy of Neurology. Neurology. 2006;66:983-995.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/28/2019
Annual Revision	**Parkinson's Disease.** Kynmobi and Ongentys were added to the Note of previously tried Parkinson's disease treatments. For patients with a trial of an oral extended-release carbidopa/levodopa therapy, wording of "unacceptable tolerability" was changed to "significant intolerance"	08/19/2020

PRIOR AUTHORIZATION POLICY

POLICY: Parkinson's Disease – Inbrija Prior Authorization Policy

- Inbrija™ (levodopa inhalation powder for oral inhalation use – Acorda)

REVIEW DATE: 08/19/2020

OVERVIEW

Inbrija, an aromatic amino acid, is indicated for the intermittent treatment of "off" episodes in patients with Parkinson's disease treated with carbidopa-levodopa.[1] Inbrija should be taken when symptoms of an "off" period start to return. The recommended dosage of Inbrija is 84 mg (two 42 mg capsules) as needed, up to five times daily. Inbrija capsules are for oral inhalation only and should be used only with the Inbrija inhaler. Inbrija capsules must not be swallowed. Patients are instructed to load one capsule into the inhaler and breathe in; then remove the used capsule and load the second capsule into the inhaler and breathe in. The Inbrija inhaler is breath-actuated by the patient.

Guidelines

The American Academy of Neurology published guidelines in 2006 on the treatment of Parkinson's disease with motor fluctuations and dyskinesia.[2] The guidelines are dated and do not include more recently approved medications. It is recommended to offer entacapone and rasagiline to reduce "off" time (Level A). Pergolide (withdrawn from the market in 2007 due to risk of valvular fibrosis), pramipexole, ropinirole, and tolcapone (used with caution; requires monitoring for hepatotoxicity) should be considered to reduce "off" time (Level B). Apokyn® (apomorphine hydrochloride injection), cabergoline, and selegiline may be used to reduce "off" time (Level C). According to the guidelines, the available evidence does not establish superiority of one medication over another in reducing "off" time (Level B). Sustained-release levodopa/carbidopa and bromocriptine should not be considered to reduce "off" time (Level C). Amantadine may be used to reduce dyskinesia (Level C).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Inbrija. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Inbrija as well as the monitoring required for adverse events and long-term efficacy, approval requires Inbrija to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Inbrija is recommended in those who meet the following criteria:

FDA-Approved Indications

242. Parkinson's Disease. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):

- **A)** Patient is currently taking carbidopa-levodopa; AND
- **B)** Patient is experiencing "off" episodes such as muscle stiffness, slow movements, or difficulty starting movements; AND
- **C)** Patient has previously tried one other treatment for "off" episodes and meets ONE of the following criteria (i or ii):
  - **i.** Patient had significant intolerance, according to the prescriber; OR
  - **ii.** Patient had inadequate efficacy, according to the prescriber; AND

  Note: Examples of treatments for "off" episodes are entacapone, rasagiline, pramipexole, ropinirole, tolcapone, Apokyn, cabergoline, selegiline, Ongentys, Kynmobi, or Xadago.
- **D)** Patient does not have asthma, chronic obstructive pulmonary disease, or other chronic underlying lung disease; AND
- **E)** Inbrija is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Inbrija is not recommended in the following situations:

233. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

728. Inbrija™ powder for inhalation [prescribing information]. Ardsley, NY: Acorda Therapeutics, Inc.; September 2019.
729. Pahwa R, Factor SA, Lyons KE, et al. Practice parameter: Treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review). Report of the quality standards subcommittee of the American Academy of Neurology. Neurology. 2006;66:983-995.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/23/2019
Annual Revision	Moved examples of treatments for "off" episodes out of the criteria for Parkinson's Disease, Patients with "Off" Episodes and into a Note.	01/29/2020
Early Annual Revision	**Parkinson's Disease.** Patients with "Off" Episodes was removed from the condition title and placed in criteria as patient is experiencing "off" episodes such as muscle stiffness, slow movements, or difficulty starting movements. For the requirement of previously tried treatments, criteria for significant intolerance and inadequate efficacy for those treatments was added. Kynmobi and Ongentys were added to the Note of previously tried Parkinson's disease medications.	08/19/2020

PRIOR AUTHORIZATION POLICY

POLICY: Parkinson's Disease – Lodosyn Prior Authorization Policy

- Lodosyn® (carbidopa tablets, generics)

REVIEW DATE: 08/19/2020

OVERVIEW

Lodosyn, an aromatic amino acid decarboxylation inhibitor, indicated for use with carbidopa-levodopa or with levodopa in the treatment of the symptoms of idiopathic Parkinson's disease (paralysis agitans), postencephalitic parkinsonism, and symptomatic parkinsonism, which may follow injury to the nervous system by carbon monoxide intoxication and/or manganese intoxication.[1]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Lodosyn. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lodosyn as well as the monitoring required for adverse events and long-term efficacy, approval requires Lodosyn to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lodosyn is recommended in those who meet the following criteria:

FDA-Approved Indications

243. Parkinson's Disease. Approve for 1 year if the patient meets both of the following criteria (A and B):
- **A)** Patient is currently receiving carbidopa/levodopa therapy; AND
- **B)** Lodosyn is being prescribed by, or in consultation with, a neurologist.

244. Postencephalitic Parkinsonism. Approve for 1 year if the patient meets both of the following criteria (A and B):
- **A)** Patient is currently receiving carbidopa/levodopa therapy; AND
- **B)** Lodosyn is being prescribed by, or in consultation with, a neurologist.

245. Symptomatic Parkinsonism. Approve for 1 year if the patient meets both of the following criteria (A and B):
- **A)** Patient is currently receiving carbidopa/levodopa therapy; AND
- **B)** Lodosyn is being prescribed by, or in consultation with, a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lodosyn is not recommended in the following situations:

234. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

730. Lodosyn® [prescribing information] Bridgewater, NJ: Aton Pharma; February 2017.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/28/2019
Annual Revision	No criteria changes.	08/19/2020

PRIOR AUTHORIZATION POLICY

POLICY: Parkinson's Disease – Nourianz Prior Authorization Policy

- Nourianz™ (istradefylline tablets – Kyowa Kirin)

REVIEW DATE: 08/19/2020

OVERVIEW

Nourianz, an adenosine receptor antagonist, is indicated as adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease experiencing "off" episodes.[1]

Guidelines

The American Academy of Neurology published guidelines in 2006 on the treatment of Parkinson's disease with motor fluctuations and dyskinesia.[2] The guidelines are dated and do not include more recently approved medications. It is recommended to offer entacapone and rasagiline to reduce "off" time (Level A). Pergolide (withdrawn from the market in 2007 due to risk of valvular fibrosis), pramipexole, ropinirole, and tolcapone (used with caution; requires monitoring for hepatotoxicity) should be considered to reduce "off" time (Level B). Apokyn® (apomorphine hydrochloride injection), cabergoline, and selegiline may be used to reduce "off" time (Level C). According to the guidelines, the available evidence does not establish superiority of one medication over another in reducing "off" time (Level B). Sustained-release levodopa/carbidopa and bromocriptine should not be considered to reduce "off" time (Level C). Amantadine may be used to reduce dyskinesia (Level C).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Nourianz. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Nourianz as well as the monitoring required for adverse events and long-term efficacy, approval requires Nourianz to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nourianz is recommended in those who meet the following criteria:

FDA-Approved Indications

246. Parkinson's Disease. Approve Nourianz for 1 year if patient meets both of the following (A and B):

F) Patient is currently taking carbidopa-levodopa; AND

G) Patient is experiencing "off" episodes such as muscle stiffness, slow movements, or difficulty starting movements; AND

H) Nourianz is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nourianz is not recommended in the following situations:

235. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

731. Nourianz™ [prescribing information]. Bedminster, NJ: Kyowa Kirin, Inc.; May 2020.

732. Pahwa R, Factor SA, Lyons KE, et al. Practice parameter: Treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review). Report of the quality standards subcommittee of the American Academy of Neurology. Neurology. 2006;66:983-995.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/09/2019
Selected Revision	In **Parkinson's Disease, Patients with "Off" Episodes,** criteria stating the "patient has tried and/or is concomitantly receiving at least one other adjunctive medication for the treatment of "off" episodes" was removed from the policy.	01/29/2020
Early Annual Revision	**Parkinson's Disease:** Patients with "Off" Episodes was removed from the condition title and placed in criteria as patient is experiencing "off" episodes such as muscle stiffness, slow movements, or difficulty starting movements.	08/19/2020

PRIOR AUTHORIZATION POLICY

POLICY: Parkinson's Disease – Nuplazid Prior Authorization Policy

- Nuplazid® (pimavanserin capsules and tablets – Acadia)

REVIEW DATE: 08/19/2020

OVERVIEW

Nuplazid, a selective serotonin 5-HT_{2A} inverse agonist, is indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.[1]

Safety

Nuplazid has a Boxed Warning regarding increased mortality in elderly patients with dementia-related psychosis.[1] Nuplazid is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Nuplazid. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with

Nuplazid as well as the monitoring required for adverse events and long-term efficacy, approval requires Nuplazid to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nuplazid is recommended in those who meet the following criteria:

FDA-Approved Indications

~~75.~~72. **Parkinson's Disease Psychosis.** Approve for 1 year if the patient meets all of the following criteria (A, B, and C):

30. Patient has hallucinations and delusions associated with Parkinson's disease pychosis; AND

31. Patient does not have dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis; AND

32. Nuplazid is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nuplazid is not recommended in the following situations:

236. Dementia-Related Psychosis. Nuplazid prescribing information has a Boxed Warning regarding increased mortality in elderly patients with dementia-related psychosis.[1] Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.

237. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

733. Nuplazid® tablets and capsules [prescribing information]. San Diego, CA: Acadia Pharmaceuticals Inc.; May 2019.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/18/2018
Update	1/16/2019: Addition of "Parkinson's Disease" to title of policy.	NA
Annual revision	No criteria changes.	07/31/2019
Annual Revision	No criteria changes.	08/19/2020

NA – Not applicable.

PRIOR AUTHORIZATION POLICY

POLICY: Parkinson's Disease – Tolcapone Products Prior Authorization Policy

- Tasmar® (tolcapone tablets, generics [100 mg strength only])

REVIEW DATE: 08/19/2020

OVERVIEW

Tolcapone, an inhibitor of catechol-O-methyltransferase, is used in the treatment of Parkinson's disease as an adjunct to levodopa/carbidopa therapy.[1]

Guidelines

The American Academy of Neurology published guidelines in 2006 on the treatment of Parkinson's disease with motor fluctuations and dyskinesia.[2] The guidelines are dated and do not include more recently approved medications. It is recommended to offer entacapone and rasagiline to reduce "off" time (Level A). Pergolide (withdrawn from the market in 2007 due to risk of valvular fibrosis), pramipexole, ropinirole, and tolcapone (used with caution; requires monitoring for hepatotoxicity) should be considered to reduce "off" time (Level B). Apokyn® (apomorphine hydrochloride injection), cabergoline, and selegiline may be used to reduce "off" time (Level C). According to the guidelines, the available evidence does not establish superiority of one medication over another in reducing "off" time (Level B). Sustained-release levodopa/carbidopa and bromocriptine should not be considered to reduce "off" time (Level C). Amantadine may be used to reduce dyskinesia (Level C).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of tolcapone products. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with tolcapone products as well as the monitoring required for adverse events and long-term efficacy, approval requires tolcapone products to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of tolcapone products is recommended in those who meet the following criteria:

FDA-Approved Indications

247. Parkinson's Disease. Approve for 1 year if the patient meets all of the following criteria (A, B, and C):

- **A)** Patient is currently receiving carbidopa/levodopa therapy; AND
- **B)** Patient has tried an entacapone product and meets ONE of the following criteria (i or ii):
  - **i.** Patient had significant intolerance, according to the prescriber; OR
  - **ii.** Patient had inadequate efficacy, according to the prescriber; AND
- **C)** Tolcapone is being prescribed by, or in consultation with, a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of tolcapone products is not recommended in the following situations:

238. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

734. Tasmar® oral tablets [prescribing information] Bridgewater, NJ: Valeant Pharmaceuticals; December 2018.
735. Pahwa R, Factor SA, Lyons KE, et al. Practice parameter: Treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review). Report of the quality standards subcommittee of the American Academy of Neurology. Neurology. 2006;66:983-995.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/28/2019
Annual Revision	**Parkinson's Disease:** For patients with a trial of entacapone, wording of "unacceptable tolerability" was changed to "significant intolerance" and "could not achieve adequate benefit" was changed to "had inadequate efficacy".	08/19/2020

PRIOR AUTHORIZATION POLICY

POLICY: Parkinson's Disease – Zelapar Prior Authorization Policy
- Zelapar® (selegiline hydrochloride tablets, orally disintegrating)

REVIEW DATE: 08/19/2020

OVERVIEW
Zelapar, an irreversible inhibitor of monoamine oxidase, is indicated as an adjunct in the management of patients with Parkinson's disease being treated with levodopa/carbidopa who exhibit deterioration in the quality of their response to this therapy.[1] Zelapar is an oral disintegrating tablet that dissolves in the mouth seconds after placement on the tongue and is rapidly absorbed.

Guidelines
The American Academy of Neurology published guidelines in 2006 on the treatment of Parkinson's disease with motor fluctuations and dyskinesia.[2] The guidelines are dated and do not include more recently approved medications. It is recommended to offer entacapone and rasagiline to reduce "off" time (Level A). Pergolide (withdrawn from the market in 2007 due to risk of valvular fibrosis), pramipexole, ropinirole, and tolcapone (used with caution; requires monitoring for hepatotoxicity) should be considered to reduce "off" time (Level B). Apokyn® (apomorphine hydrochloride injection), cabergoline, and selegiline may be used to reduce "off" time (Level C). According to the guidelines, the available evidence does not establish superiority of one medication over another in reducing "off" time (Level B). Sustained-release levodopa/carbidopa and bromocriptine should not be considered to reduce "off" time (Level C). Amantadine may be used to reduce dyskinesia (Level C).

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Zelapar. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zelapar as well as the monitoring required for adverse events and long-term efficacy, approval requires Zelapar to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Zelapar is recommended in those who meet the following criteria:

FDA-Approved Indications

248. Parkinson's Disease. Approve for 1 year if the patient meets all of the following criteria (A, B, C, and D):
- **A)** Patient is experiencing "off" episodes such as muscle stiffness, slow movements, or difficulty starting movements; AND
- **B)** Patient is currently receiving carbidopa/levodopa therapy; AND
- **C)** Patient has tried one of the oral selegiline tablets, selegiline capsules, or rasagiline tablets and meets ONE of the following criteria (i or ii):
  - **i.** Patient had significant intolerance, according to the prescriber; OR
  - **ii.** Patient has difficulty swallowing tablets or capsules; AND
- **D)** Zelapar is being prescribed by, or in consultation with, a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zelapar is not recommended in the following situations:

239. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

736. Zelapar® orally disintegrating tablets [prescribing information] Bridgewater, NJ: Valeant Pharmaceuticals; February 2020.
737. Pahwa R, Factor SA, Lyons KE, et al. Practice parameter: Treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review). Report of the quality standards subcommittee of the American Academy of Neurology. Neurology. 2006;66:983-995.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/28/2019
Selected Revision	**Parkinson's Disease:** For the criteria requiring a patient has tried oral selegiline tablets, selegiline capsules and rasagiline tablets were added as options.	04/08/2020
Annual Revision	**Parkinson's Disease:** For patients with a trial of oral selegiline tablets, selegiline capsules, or rasagiline tablets, wording of "unacceptable tolerability" was changed to "significant intolerance".	08/19/2020

PRIOR AUTHORIZATION POLICY

POLICY: Parkinson's Disease – Kynmobi Prior Authorization Policy

- Kynmobi™ (apomorphine sublingual film – Sunovion Pharmaceuticals)

REVIEW DATE: 07/15/2020; selected revision 08/19/2020; selected revision 10/21/2020

OVERVIEW

Kynmobi, a non-ergoline dopamine agonist, is indicated for the acute, intermittent treatment of "off" episodes in patients with Parkinson's disease.[1]

Guidelines

The American Academy of Neurology published guidelines in 2006 on the treatment of Parkinson's disease with motor fluctuations and dyskinesia.[2] The guidelines are dated and do not include more recently approved medications, including Kynmobi. It is recommended to offer entacapone and rasagiline to reduce "off" time (Level A). Pergolide (withdrawn from the market in 2007 due to risk of valvular fibrosis), pramipexole, ropinirole, and tolcapone (used with caution; requires monitoring for hepatotoxicity) should be considered to reduce "off" time (Level B). Apokyn® (apomorphine hydrochloride injection), cabergoline, and selegiline may be used to reduce "off" time (Level C). According to the guidelines, the available evidence does not establish superiority of one medication over another in reducing "off" time (Level B). Sustained-release levodopa/carbidopa and bromocriptine should not be considered to reduce "off" time (Level C). Amantadine may be used to reduce dyskinesia (Level C).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Kynmobi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Kynmobi as well as the monitoring required for adverse events and long-term efficacy, approval requires Kynmobi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kynmobi is recommended in those who meet the following criteria:

FDA-Approved Indications

249. Parkinson's Disease. Approve for 1 year if the patient meets all of the following criteria (A, B, C, and D):

A) Patient is experiencing "off" episodes such as muscle stiffness, slow movements, or difficulty starting movements; AND

B) Patient is currently receiving carbidopa/levodopa therapy; AND

C) Patient has previously tried one other treatment for "off" episodes and meets ONE of the following criteria (i or ii):

i. Patient had significant intolerance, according to the prescriber; OR

ii. Patient had inadequate efficacy, according to the prescriber; AND

Note: Examples of treatment for "off" episodes include entacapone, rasagiline, pramipexole, ropinirole, tolcapone, cabergoline, Ongentys, selegiline, Xadago.

D) Kynmobi is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kynmobi is not recommended in the following situations:

240. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

738. Kynmobi™ sublingual film [prescribing information]. Marlborough, MA: Sunovion Pharmaceuticals; May 2020.

739. Pahwa R, Factor SA, Lyons KE, et al. Practice parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review). Report of the quality standards subcommittee of the American Academy of Neurology. *Neurology*. 2006;66:983-995.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/15/2020
Selected Revision	**Parkinson's Disease:** For the requirement of previously tried treatments, the number of medications was changed from two treatments to one and criteria for significant intolerance and inadequate efficacy for those treatments was added. Ongentys was added to the Note of previously tried Parkinson's disease treatments.	08/19/2020
Selected Revision	**Parkinson's Disease.** The requirement for the patient to have advanced Parkinson's disease was removed from criteria.	10/21/2020

PRIOR AUTHORIZATION POLICY

POLICY: Parkinson's Disease – Ongentys Prior Authorization Policy

- Ongentys® (opicapone capsules – Neurocrine Biosciences)

REVIEW DATE: 07/15/2020; selected revision 08/19/2020

OVERVIEW

Ongentys, a peripheral, selective and reversible catechol-o-methyltransferase inhibitor, is indicated for adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease experiencing "off" episodes.[1]

Guidelines

The American Academy of Neurology published guidelines in 2006 on the treatment of Parkinson's disease with motor fluctuations and dyskinesia.[2] The guidelines are dated and do not include more recently approved medications, including Ongentys. It is recommended to offer entacapone and rasagiline to reduce "off" time (Level A). Pergolide (withdrawn from the market in 2007 due to risk of valvular fibrosis), pramipexole, ropinirole, and tolcapone (used with caution; requires monitoring for hepatotoxicity) should be considered to reduce "off" time (Level B). Apokyn® (apomorphine hydrochloride injection), cabergoline, and selegiline may be used to reduce "off" time (Level C). According to the guidelines, the available evidence does not establish superiority of one medication over another in reducing "off" time (Level B). Sustained-release levodopa/carbidopa and bromocriptine should not be considered to reduce "off" time (Level C). Amantadine may be used to reduce dyskinesia (Level C).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ongentys. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ongentys as well as the monitoring required for adverse events and long-term efficacy, approval requires Ongentys to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ongentys is recommended in those who meet the following criteria:

FDA-Approved Indications

250. Parkinson's Disease. Approve for 1 year if the patient meets all of the following criteria (A, B, and C):
- **A)** Patient is currently receiving carbidopa/levodopa therapy; AND
- **B)** Patient meets ONE of the following criteria (i or ii):
  - **i.** Patient has tried an entacapone product and meets ONE of the following criteria (a or b):
    - **a)** Patient had significant intolerance, according to the prescriber; OR
    - **b)** Patient had inadequate efficacy, according to the prescriber; OR
  - **ii.** Patient is currently receiving Ongentys; AND
- **C)** Ongentys is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ongentys is not recommended in the following situations:

241. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

740. Ongentys® capsules [prescribing information]. San Diego, CA: Neurocrine Biosciences; May 2020.
741. Pahwa R, Factor SA, Lyons KE, et al. Practice parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review). Report of the quality standards subcommittee of the American Academy of Neurology. *Neurology*. 2006;66:983-995.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/15/2020
Selected Revision	**Parkinson's Disease.** For patients currently receiving Ongentys therapy, criteria was added to allow for continuation without trial of entacapone. For patients with a trial of entacapone, wording of "unacceptable tolerability" was changed to "significant intolerance" and "could not achieve adequate benefit" was changed to "had inadequate efficacy".	08/19/2020

PRIOR AUTHORIZATION POLICY

POLICY: Pegylated Interferons
- Pegasys® (peginterferon alfa-2a injection for subcutaneous use – Hoffman-La Roche/Genentech)
- PegIntron® (peginterferon alfa-2b injection for subcutaneous use – Schering)

TAC APPROVAL DATE: 08/28/2019

OVERVIEW

Pegasys and PegIntron are pegylated interferons (peginterferons) indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults and children.[1-2] The standard of care in hepatitis C is rapidly evolving and the place in therapy for peginterferon very small. The approval of direct-acting antiviral agents (DAAs) has eliminated the need for peginterferon in the majority of patients. Because none of the DAAs are indicated in pediatric patients, peginterferons still have a role in the treatment of pediatric patients

with HCV. In the past, the standard of care for patients with HCV consisted of peginterferon and ribavirin (PR) generally administered for 24 to 48 weeks depending on patient factors and genotype.

Clinical Efficacy Data

The clinical efficacy of peginterferon(in combination with ribavirin) has been demonstrated in a variety of clinical settings: treatment-naïve patients, patients previously treated with peginterferon or interferon for hepatitis C, pediatric patients with hepatitis C, and in other special populations including patients with human immunodeficiency virus (HIV) co-infection, cirrhosis/fibrosis, and in patients slow to respond to therapy. In addition, the peginterferons have also been studied in combination with the DAAs (these studies are detailed in the *Hepatitis C Direct-Acting Antiviral Therapy Class Summary*).

None of the DAAs are indicated in pediatric patients < 18 years of age. Pegasys (alone or in combination with ribavirin) and PegIntron (in combination with ribavirin) are indicated for the treatment of chronic HCV in patients ≥ 5 years and ≥ 3 years of age, respectively with compensated liver disease previously untreated with interferon alfa.[1-2] Limited data are available for retreatment in children.

Guidelines

For a summary of American Association for the Study of Liver Diseases (AASLD) guidelines please see *Hepatitis C Direct-Acting Antiviral Therapy Class Summary*. In summary, peginterferons are no longer recommended.[3]

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) practice guidelines for the diagnosis and management of hepatitis C infection in infants, children and adolescents (2012) recommend that children with hepatitis C who demonstrate persistently elevated serum aminotransferases or those with progressive disease (i.e., liver fibrosis) should be considered for treatment.[4] The NASPGHAN guidelines state that the recommended therapy for children ages 3 to 17 years of age is with PR. The recommended length of therapy is 48 weeks for children with genotype 1 or 4 CHC and 24 weeks for genotype 2 or 3 CHC. In children and adolescents, NASPGHAN recognizes that although rare in children, pediatric liver transplant recipients for end-stage liver disease (ESLD) due to chronic HCV demonstrate allograft survival rates of 72% and 55%, respectively, at 5 years.[4] Following re-transplantation, these rates decrease to 55% and 34%, respectively. The risk of HCV recurrence in pediatric orthotopic liver transplant recipients is high and is associated with a high rate of re-transplantation. If a decision is made to treat pediatric liver transplant recipients, very close monitoring is warranted.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Pegasys and PegIntron (collectively referred to as "peginterferons" in these criteria) for HCV infection. The intent of this policy is to provide recommendations for use in hepatitis C *only*. Because of the specialized skills required for evaluation and diagnosis of patients treated with the peginterferons as well as the monitoring required for adverse events (AEs) and efficacy, approval requires peginterferons to be prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or liver transplant physician. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Pegasys and PegIntron ("peginterferon[s]") is recommended in patients who meet one of the criteria below (1 through 6).

FDA-Approved Indications

1. **Chronic Hepatitis C Virus (HCV) Genotype 1, 2, 3, 4, 5, or 6.** Approve peginterferon for up to 48 weeks in patients who meet ALL of the following criteria (A, B, and C):
   A) The patient is ≥ 2 years of age; AND
   B) Peginterferon is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or liver transplant physician; AND
   C) Peginterferon is prescribed in combination with ribavirin.

Other Uses with Supportive Evidence (in the Treatment of Hepatitis C)

2. **Recurrent Hepatitis C Virus (HCV) Post-Liver Transplantation, Pediatric and Adolescent (≥ 2 years and ≤ 17 years of age).** Approve peginterferon for 48 weeks in patients who meet ALL of the following criteria (A, B, and C):
   A) The patient is ≥ 2 years of age and < 17 years of age; AND
   B) Peginterferon is prescribed by or in consultation with one of the following prescribers who is affiliated with a transplant center: a gastroenterologist, hepatologist, infectious diseases physician, or liver transplant physician; AND
   C) Peginterferon is prescribed in combination with ribavirin unless there is a contraindication or intolerance to ribavirin according to the prescribing physician.

   In the opinion of specialist physicians reviewing the data, we have adopted these criteria.

3. **Chronic Hepatitis C Virus (HCV) – Awaiting Liver Transplantation, Any Viral Genotype - Pediatric and Adolescents (≥ 2 years and ≤ 17 years of age).** Approve peginterferon for 12 months in patients who meet ALL of the following criteria (A, B, and C).
   A) The patient is ≥ 2 years of age and ≤ 17 years of age; AND
   B) Peginterferon is prescribed by or in consultation with one of the following prescribers who is affiliated with a liver transplant center: a gastroenterologist, hepatologist, infectious diseases physician, or liver transplant physician; AND
   C) Peginterferon is prescribed in combination with ribavirin unless there is a contraindication or intolerance to ribavirin according to the prescribing physician.

4. **Patient has Been Started on Pegasys.** Approve for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications or Other Uses with Supportive Evidence). Authorization duration will vary based on the indication but should not exceed a total duration of 12 months.

5. **Patient has Been Started on PegIntron.** Approve for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications or Other Uses with Supportive Evidence). Authorization duration will vary based on the indication but should not exceed a total duration of 12 months.

6. **Indications other than Hepatitis C.** Approve for 12 months. Pegasys and PegIntron have been used for many off-label indications in adults and for few indications in children.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

The peginterferons have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Hepatitis C Virus (HCV), Maintenance Therapy.** Evidence does not support use. Major published trials have failed to demonstrate a consistent benefit of maintenance therapy in the prevention of hepatocellular carcinoma (HCC).[3-7]

   In the opinion of a specialist physician reviewing the data, we have adopted this criterion.

2. **Life Expectancy < 12 Months Due to Non-Liver Related Co-Morbidities.** Patients with a limited life expectancy that cannot be remediated by HCV treatment, liver transplantation, or another directed therapy do not require antiviral treatment.[3] Patients with a short life expectancy owing to liver disease should be managed in consultation with an expert. Little evidence exists to support initiation of HCV treatment in patients with a limited life expectancy (< 12 months) owing to non-liver-related comorbid conditions. For these patients, the benefits of HCV treatment are unlikely to be realized and palliative care strategies should take precedence.

REFERENCES

1. Pegasys® injection [package insert]. Nutley, NJ: Hoffman-La Roche Pharmaceuticals; October 2017.
2. PegIntron® powder for injection [package insert]. Kenilworth, NJ: Schering Corporation; January 2019.
3. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. Testing, managing, and treating hepatitis C. Updated May 24, 2018. Available at: http://www.hcvguidelines.org. Accessed on: August 21, 2019.
4. Mack CL, Gonzalez-Peralta RP, Gupta N, et al. North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Practice Guidelines: Diagnosis and Management of Hepatitis C Infection in Infants, Children and Adolescents. *J Pediatr Gastroenterol Nutr*. 2012;54(6):838-55.
5. Sherman KE, Anderson JW, Butt A, et al for the AIDS Clinical Trials Group A5178 Study Team. Sustained long-term antiviral maintenance therapy in HCV/HIV co-infected patients (SLAM-C). *J Aquir Immune Defic Syndr.* 2010;55(5):597-605
6. Lok AS, Everhart JE, Wright EC, et al; HALT-C Trial Group. Maintenance peginterferon therapy and other factors associated with hepatocellular carcinoma in patients with advanced hepatitis C. *Gastroenterology*. 2011;140(3):840-849.
7. Di Bisceglie AM, Stoddard AM, Dienstag JL, et al; and The HALT-C Trial group. Excess mortality in patients with advanced chronic hepatitis C treated with long-term peginterferon. *Hepatology.* 2011;53(4):1100-1108.

History

Type of Revision	Summary of Changes*	TAC Approval Date
Itegrated Policy	--	06/12/2012
Selected Revision	--	08/29/2012
Annual Revision	--	06/05/2013
Annual Revision	1. Genotype 1,4,5,6**:** Reference to "treatment-naïve" was removed; the "note" that a Week 12 titer is needed to determine therapy beyond 48 weeks was removed; a liver transplant physician was added to the list of prescribers. 2. Genotype 2, 3: Reference to "treatment-naïve" was removed; a liver transplant physician was added to the list of prescribers; a 48-week approval was removed for patients with HBV co-infection, HIV co-infection, and genotype 3 with high viral load or fibrosis/cirrhosis. 3. Retreatment: This indication was removed and these patients are encompassed in criteria based on genotype (note: patients with genotype 2, 3 no longer are approved for 48 weeks for re-treatment). 4. Extending therapy for 72 weeks (Genotype 1, 4, 5, 6): This indication was removed. Acute Hepatitis C: A liver transplant physician was added to the list of prescribers. 5. Recurrent HCV: "or in consultation with one of the following prescribers who is affiliated with a transplant center" was added; the requirement for patients to have grade 2 fibrosis or greater was removed. 6. Patients awaiting liver transplant: "or in consultation with one of the following prescribers who is affiliated with a transplant center" was added. 7. Patients already started on Pegasys or PegIntron. The authorization was changed not to exceed 48 weeks (previously 72 weeks).	06/25/2014
Selected revision	Limitations on who to treat were added to the following approval indications: Genotype 1, 2, 3, 4, 5, and 6 CHC adults. Criteria for children 2 through 17 years of age are addressed separately. Exclusion criteria were added for patients with life expectancy < 12 months due to a non-liver related cause.	09/10/2014
Annual revision	1. Chronic Hepatitis C (CHC) Genotype 1, 4, 5, or 6 Chronic Hepatitis C (CHC) – Adults (≥ 18 years of age). -Patients with genotype 1 CHC taking pegylated interferon in combination with Olysio: The approval duration is 48 weeks for prior null or partial responders and 24 weeks for treatment-naïve or relapse patients. -Patients with genotype 1, 4, 5, or 6 CHC taking pegylated interferon in combination with Sovaldi. The approval duration is 12 weeks. -The exception to using ribavirin in combination with pegylated interferon in patients with a contraindication or intolerance to ribavirin according to the prescribing physician was removed from the criteria. 2. CHC Genotype 2 or 3 – Adults (≥ 18 years of age). The approval duration was changed to 12 weeks. A requirement was added that patients take pegylated interferon with Sovaldi and ribavirin (previously ribavirin only), and criteria allowing exceptions for using ribavirin were removed. 3. Acute Hepatitis C (i.e., Infection within 6 Months of Exposure). The timeframe patients must wait prior to treatment to allow for spontaneous resolution was changed to 12 weeks (previously 8 weeks). 4. Recurrent HCV Post-Liver Transplantation, Any Viral Genotype. This indication was changed to "Recurrent HCV Post-Liver Transplantation", "any viral genotype" was removed. For patients ≥	07/15/2015

	18 years of age, this indication is only approved for genotypes 5 and 6 (previously all genotypes were approved). For patients ≥ 2 years of age and ≤ 17 years of age, any viral genotype continues to be approved. 5. CHC – Awaiting Liver Transplantation, Any Viral Genotype. This indication was modified to "CHC – Awaiting Liver Transplantation, Any Viral Genotype - Pediatric and Adolescents (≥ 2 years and ≤ 17 years of age)". The criterion for age was changed to only approve in patients ≥ 2 years and ≤ 17 years of age.	
Annual revision	Genotype 1, 4, 5, or 6 chronic HCV, adults: -Added genotype 2 or 3 chronic HCV to this indication (previously, this was a separate indication). -Approval duration changed from 12 to 48 weeks to up to 48 weeks. -Age requirement changed from ≥ 18 years to ≥ 2 years of age. -Requirement for Metavir score F3/F4 or exceptions to Metavir score removed. -Requirement for concomitant therapy (Olysio or Sovaldi) removed from the policy. Genotype 1, 4, 5, or 6 chronic HCV, pediatric and adolescent: -This indication was combined with the prior adult indication (as detailed above). Genotype 2 or 3 chronic HCV, adults: -This indication was combined with genotype 1, 4, 5, and 6 chronic HCV (see above). -Approval duration changed from 12 weeks to up to 48 weeks. -Age requirement changed from ≥ 18 years to ≥ 2 years of age. -Requirement for Metavir score F3/F4 or exceptions to Metavir score removed. Genotype 2 or 3 chronic HCV, pediatric and adolescent: -This indication was combined with genotype 1, 4, 5, and 6 chronic HCV (see above). -Approval duration changed from 24 or 48 weeks to up to 48 weeks. Acute Hepatitis C: - This indication was removed from the policy.	08/10/2016
Annual Revision	No criteria changes	08/16/2017
Annual Revision	Recurrent Hepatitis C Virus (HCV) Post-Liver Transplantation: Criteria to approve in adults with genotypes 5 and 6 were removed.	08/15/2018

TAC – Therapeutic Assessment Committee; DEU – Drug Evaluation Unit; * For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx; HIV – Human immunodeficiency virus; HBV – Hepatitis B virus; HCV – Hepatitis C virus.

PRIOR AUTHORIZATION POLICY

POLICY: Pegylated Interferons Prior Authorization Policy

- Pegasys® (peginterferon alfa-2a injection for subcutaneous use – Hoffman-La Roche/Genentech)
- PegIntron® (peginterferon alfa-2b injection for subcutaneous use – Schering)

REVIEW DATE: 10/14/2020

OVERVIEW

Pegasys and PegIntron are pegylated interferons (peginterferons) indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults and children.[1-2] Pegasys (alone or in combination with ribavirin)

and PegIntron (in combination with ribavirin) are indicated for the treatment of chronic HCV in patients ≥ 5 years of age and ≥ 3 years of age, respectively, with compensated liver disease previously untreated with interferon alfa. In the past, the standard of care for patients with HCV consisted of peginterferon and ribavirin generally administered for 24 to 48 weeks depending on patient factors and genotype. However, with the approval of direct-acting antivirals, pegylated interferons no longer have a role in the management of HCV for adults or pediatric patients.

Guidelines

Peginterferons are no longer addressed by the American Association for the Study of Liver Diseases recommendations for testing, managing, and treating HCV.[3] Further, direct-acting antiviral treatment with an approved regimen is recommended for all children and adolescents with HCV infection ≥ 3 years of age as they will benefit from antiviral therapy, regardless of disease severity.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Pegasys and PegIntron (collectively referred to as "peginterferons" in these criteria) for HCV infection. The intent of this policy is to provide recommendations for use in **hepatitis C *only***. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with the peginterferons as well as the monitoring required for adverse events AEs and efficacy, approval requires peginterferons to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Pegasys and PegIntron (peginterferon[s]) is recommended in those who meet the following criteria:

FDA-Approved Indications

251. Chronic Hepatitis C Virus (HCV) Genotype 1, 2, 3, 4, 5, or 6. Approve for up to 48 weeks in patients who meet all of the following criteria (A, B, and C):
- **A)** Patient is ≥ 2 years of age; AND
- **B)** The medication is prescribed in combination with ribavirin; AND
- **C)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or liver transplant physician.

Other Uses with Supportive Evidence (in the Treatment of Hepatitis C)

252. Recurrent Hepatitis C Virus (HCV) Post-Liver Transplantation, Pediatric and Adolescent (≥ 2 Years and ≤ 17 Years of Age). Approve for 48 weeks in patients who meet all of the following criteria (A, B, and C):
- **A)** Patient is ≥ 2 years of age and < 17 years of age; AND
- **B)** The medication is prescribed in combination with ribavirin unless there is a contraindication or intolerance to ribavirin according to the prescriber; AND
- **C)** The medication is prescribed by or in consultation with one of the following prescribers who is affiliated with a transplant center: a gastroenterologist, hepatologist, infectious diseases physician, or liver transplant physician.

253. Chronic Hepatitis C Virus (HCV) – Awaiting Liver Transplantation, Any Viral Genotype - Pediatric and Adolescents (≥ 2 years and ≤ 17 years of age). Approve for 12 months in patients who meet all of the following criteria (A, B, and C):
- **A)** Patient is ≥ 2 years of age and ≤ 17 years of age; AND

B) The medication is prescribed in combination with ribavirin unless there is a contraindication or intolerance to ribavirin according to the prescriber; AND

C) The medication is prescribed by or in consultation with one of the following prescribers who is affiliated with a liver transplant center: a gastroenterologist, hepatologist, infectious diseases physician, or liver transplant physician.

254. Patient has Been Started on Pegasys. Approve for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications or Other Uses with Supportive Evidence). Authorization duration will vary based on the indication but should not exceed a total duration of 12 months.

255. Patient has Been Started on PegIntron. Approve for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications or Other Uses with Supportive Evidence). Authorization duration will vary based on the indication but should not exceed a total duration of 12 months.

256. Indications Other Than Hepatitis C. Approve for 12 months. Pegasys and PegIntron have been used for many off-label indications in adults and for few indications in children.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Pegasys and PegIntron (peginterferon[s]) is not recommended in the following situations:

1. **Hepatitis C Virus (HCV), Maintenance Therapy.** Evidence does not support use. Major published trials have failed to demonstrate a consistent benefit of maintenance therapy in the prevention of hepatocellular carcinoma (HCC).[3-7]

2. **Life Expectancy < 12 Months Due to Non-Liver Related Co-Morbidities.** Patients with a limited life expectancy that cannot be remediated by HCV treatment, liver transplantation, or another directed therapy do not require antiviral treatment.[3] Patients with a short life expectancy owing to liver disease should be managed in consultation with an expert. Little evidence exists to support initiation of HCV treatment in patients with a limited life expectancy (< 12 months) owing to non-liver-related comorbid conditions. For these patients, the benefits of HCV treatment are unlikely to be realized and palliative care strategies should take precedence.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Recurrent Hepatitis C Virus (HCV) Post-Liver Transplantation: Criteria to approve in adults with genotypes 5 and 6 were removed.	08/15/2018
Annual Revision	No criteria changes	08/29/2019
Annual Revision	Recurrent Hepatitis C Virus (HCV) Post-Liver Transplantation, Pediatric and Adolescent (≥ 2 Years and ≤ 17 Years of Age). Reference to prescribing physician was changed to prescriber. Chronic Hepatitis C Virus (HCV) – Awaiting Liver Transplantation, Any Viral Genotype - Pediatric and Adolescents (≥ 2 years and ≤ 17 years of age). Reference to prescribing physician was changed to prescriber.	10/14/2020

PRIOR AUTHORIZATION POLICY

POLICY: Phenylketonuria – Kuvan® (sapropterin dihydrochloride tablets and powder for oral solution – BioMarin Pharmaceuticals) Prior Authorization Policy

REVIEW DATE: 06/17/2020

OVERVIEW

Kuvan is indicated to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-(BH4) responsive phenylketonuria (PKU).[1] The medication should be used with a Phe-restricted diet. Kuvan works by increasing phenylalanine hydroxylase (PAH). It is a synthetic preparation of naturally occurring BH4, which is a cofactor for the enzyme PAH. PAH hydroxylates Phe in an oxidative reaction to form tyrosine. In patients with PKU, PAH activity is deficient or absent. Treatment with BH4 can activate residual PAH enzyme, improve the normal oxidative metabolism of Phe, and decrease Phe levels in some patients.

PKU is the most prevalent disorder due to an inborn error in amino acid metabolism.[3] It is caused by mutations in the PAH gene.[3] The annual incidence is about 1:15,000 births in the US. Genotypes of the disease range from a mild increase in blood Phe concentrations to a severe classic phenotype with very pronounced increases in HPA, which if not treated, can result in profound and irreversible mental disability.[3] Dietary restrictions in Phe are a mainstay in PKU management. Patients with PKU have to intake Phe-free formula and avoid foods that are protein-rich (e.g., meats, fish, eggs, standard bread, most cheeses, nuts and seeds). Other foods and beverages that contain aspartame, flour, soy, beer, or cream should be avoided. Low-protein foods that are natural may be consumed in restricted amounts, such as potatoes, some vegetables, and most cereals. During infancy, adherence to dietary restrictions is more manageable but as children grow older and become adults the dietary limitations can become burdensome.

Dose Titration

In patients with PKU who are responsive to treatment, blood Phe levels decrease within 24 hours after administration, although maximal effect on Phe levels may take up to 1 month. Blood Phe levels should be checked after 1 week of treatment and periodically for 1 month. If blood Phe does not decrease from baseline at the 10 mg/kg/day dose, the dose may be increased to 20 mg/kg/day. Patients whose blood Phe does not decrease after 1 month of treatment at 20 mg/kg/day are non-responders and treatment with Kuvan should be discontinued. Once responsiveness has been determined, the dose may be adjusted within the range of 5 to 20 mg/kg/day.

Guidelines/Recommendations

According to the European guidelines for phenylketonuria (2017), there is consensus in the literature that patients with blood phenylalanine concentration > 600 µmol/L should be treated.[8] There is also consensus that patients with blood Phe concentration < 360 µmol/L can remain untreated, but should be monitored.

Patients with blood Phe concentration between 360 to 600 µmol/L should be treated until 12 years of age. Treatment for life is recommended for any patient with PKU; however, it is also noted that patients ≥ 12 years of age with blood Phe concentration < 600 µmol/L do not require treatment. All adults with PKU should have lifelong systematic follow-ups in specialized metabolic centers, due to specific risks which may occur during adulthood. With regards to target Phe levels, in treated PKU patients up to 12 years of age, the target Phe levels should be 120 to 360 µmol/L; in treated PKU patients ≥ 12 years of age, the target Phe levels should be 120 to 600 µmol/L.

The American College of Medical Genetics and Genomics (ACMG) published practice guidelines (2014) for the diagnosis and management of PAH deficiency.[9] The guidelines recommend initiating treatment as early as possible, preferably within the first week of life with a goal of having blood Phe levels in the treatment range within the first 2 weeks. Dietary restriction of Phe intake is the mainstay of therapy for PKU. Blood Phe levels in all patients should be maintained in the range of 120 to 360 µmol/L. Newly diagnosed infants should be monitored at least weekly for their levels at least until 1 year of age. For children 1 through 12 years of age, biweekly to monthly monitoring of levels is adequate and for adolescents and adults who are stable and well-controlled, monthly testing is usually adequate. The guidelines state that approximately 25% to 50% of patients with PAH deficiency are responsive to Kuvan. A significant decline in blood Phe level is expected in responders once treatment is initiated (with Phe-restricted diet); however, patients in the lower end of the treatment range (≤ 180 µmol/L) rarely show a decrease in blood Phe level even if they are responsive to Kuvan. In these patients, responsiveness is determined by adding Phe to the diet in a stepwise method. An improvement in neuropsychiatric symptoms or increase in Phe tolerance without a decrease in blood Phe levels is sufficient reasoning to continue therapy. According to the guidelines, there is strong evidence to support life-long treatment and maintenance of metabolic control in patients with PAH deficiency.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Kuvan tablets and powder for oral solution. Because of the specialized skills required for evaluation and diagnosis of patients treated with Kuvan as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Kuvan to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 1 year in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kuvan tablets or Kuvan powder for oral solution is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Phenylketonuria.** Approve for the duration noted if the patient meets the following criteria (A or B):
   - **A)** Initial Therapy: Approve for 12 weeks if the patient meets the following criteria (i and ii):
     - **i.** Kuvan is prescribed in conjunction with a phenylalanine (Phe)-restricted diet; AND
     - **ii.** The medication is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).
   - **B)** Patients Continuing Therapy: Approve for 1 year if the patient meets the following criteria (i and ii):

     Note: Patients who have received < 12 weeks of therapy or those who are restarting therapy with Kuvan should be considered under criterion 1A (Phenylketonuria – Initial Therapy).

i. The patient meets one of the following (a, b, or c):
   a) The patient has had a clinical response (e.g., cognitive and/or behavioral improvements) as determined by the prescriber; OR
   b) The patient has achieved a ≥ 20% reduction in blood phenylalanine concentration from pre-treatment baseline (i.e., blood phenylalanine concentration before starting Kuvan therapy); OR
   c) Treatment with Kuvan has resulted in an increase in dietary phenylalanine tolerance, according to the prescriber; AND

ii. The patient is not receiving concomitant Palynziq.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Kuvan has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

12. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	No criteria changes	04/25/2018
Selected revision	Added "[Maintenance Therapy]" qualifier to patients continuing Kuvan indication. Added "pre-treatment" before baseline in patients continuing therapy criteria. Also defined pre-treatment baseline as prior to starting Kuvan therapy. Under Conditions Not Recommended for Approval, added concomitant therapy with Palynziq and Kuvan.	05/30/2018
Annual revision	No criteria changes	05/15/2019
Annual revision	**Phenylketonuria – Initial Therapy:** The approval condition was re-worded as listed; previously this was titled "Hyperphenylalaninemia due to Phenylketonuria – Initial Therapy".	06/17/2020

	Phenylketonuria – Patients Continuing Therapy: The approval condition was re-worded as listed; previously this was titled "Hyperphenylalaninemia due to Phenylketonuria – Patients Continuing Therapy (Maintenance Therapy)". A note was added that patients who have received less than 12 weeks of Kuvan or who are restarting Kuvan should refer to Initial Therapy criteria. "Prescribing physician" was updated to "prescriber" throughout criteria. A criterion was added allowing continued use of Kuvan if treatment with Kuvan has resulted in an increase in dietary phenylalanine concentration, according to the prescriber. Additionally, a criterion was added that concomitant use of Palynziq is not permitted (previously this was addressed under Conditions Not Recommended for Approval). **Concomitant Therapy with Kuvan and Palynziq® (pegvaliase-pqpz for injection):** Removed from policy. This is now addressed in criteria under the approval condition of "Phenylketonuia – Patients Continuing Therapy".	

PRIOR AUTHORIZATION POLICY

POLICY: Phenylketonuria – Palynziq® (pegvaliase-pqpz injection for subcutaneous use – BioMarin Pharmaceuticals) Prior Authorization Policy

REVIEW DATE: 06/17/2020

OVERVIEW

Palynziq is indicated to reduce blood phenylalanine concentrations in adult patients with phenylketonuria (PKU) who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L (µmol/L) on existing management.[1] Treatment with Palynziq should be managed by a healthcare provider experienced in the management of PKU. Baseline blood phenylalanine concentrations should be obtained before initiating treatment.

Dose Titration

Palynziq is titrated up over a period of 9 weeks to the maintenance dose of 20 mg administered subcutaneously (SC) once daily (QD). Therapeutic response may not be achieved until the patient is titrated to an effective maintenance dosage. Palynziq 20 mg SC QD should be maintained for at least 24 weeks. The dose can be increased to a maximum dose of Palynziq 40 mg SC QD in patients who have been maintained continuously on the 20 mg QD dose for at least 24 weeks and who have not achieved either a 20% reduction in blood phenylalanine concentration from pre-treatment baseline levels or a blood phenylalanine concentration ≤ 600 µmol/L. Palynziq should be discontinued in patients who have not achieved a response after 16 weeks of continuous treatment with the maximum dosage of 40 mg QD. In patients who experience blood phenylalanine concentrations < 30 µmol/L during the titration and maintenance phase, the dosage of Palynziq may be reduced and/or dietary protein and phenylalanine intake may be modified to maintain phenylalanine levels within a clinically acceptable range and above 30 µmol/L. Because of the risk of anaphylaxis Palynziq is available only through a restricted Risk Evaluation and Mitigation Strategy (REMS) program. It was unclear from the Palynziq clinical trials if all patients had tried and were non-responders to Kuvan.

Guidelines/Recommendations

The American College of Medical Genetics and Genomics (ACMG) published practice guidelines (2014) for the diagnosis and management of phenylalanine hydroxylase (PAH) deficiency.[2] The guidelines recommend initiating treatment as early as possible, preferably within the first week of life. Dietary restriction of phenylalanine intake is the mainstay of therapy for PKU. Blood phenylalanine levels in all

patients should be maintained in the range of 120 to 360 µmol/L. The guidelines state that approximately 25% to 50% of patients with PAH deficiency are responsive to Kuvan™ (sapropterin dihydrochloride tablets and powder for oral solution). A significant decline in blood phenylalanine level is expected in responders once treatment is initiated (with phenylalanine-restricted diet). An improvement in neuropsychiatric symptoms or increase in phenylalanine tolerance without a decrease in blood levels is sufficient reasoning to continue therapy. According to the guidelines, there is strong evidence to support life-long treatment and maintenance of metabolic control in patients with PAH deficiency.

According to the European guidelines for phenylketonuria (2017), there is consensus in the literature that patients with blood phenylalanine concentration > 600 µmol/L should be treated.[3] There is also consensus that patients with blood Phe concentration < 360 µmol/L can remain untreated, but should be monitored. Patients with blood Phe concentration between 360 to 600 µmol/L should be treated until 12 years of age. Treatment for life is recommended for any patient with PKU; however, it is also noted that patients ≥ 12 years of age with blood Phe concentration < 600 µmol/L do not require treatment. All adults with PKU should have lifelong systematic follow-ups in specialized metabolic centers, due to specific risks which may occur during adulthood. With regards to target Phe levels, in treated PKU patients up to 12 years of age, the target Phe levels should be 120 to 360 µmol/L; in treated PKU patients ≥ 12 years of age, the target Phe levels should be 120 to 600 µmol/L.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Palynziq. Because of the specialized skills required for evaluation and diagnosis of patients treated with Palynziq as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Palynziq to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 1 year in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Palynziq is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Phenylketonuria.** Approve for the duration noted if the patient meets one of the following (A or B):
   - **A)** Initial Therapy: Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
     - **i.** The patient is ≥ 18 years of age; AND
     - **ii.** The patient has uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on at least one existing treatment modality; AND
       Note: Examples of treatment modalities include restriction of dietary phenylalanine and protein intake and prior treatment with Kuvan (sapropterin dihydrochloride tablets and powder for oral solution).
     - **iii.** The medication is prescribed by or in consultation with a metabolic disease specialist (or specialist who focuses in the treatment of metabolic diseases).
   - **B)** Patients Continuing Therapy: Approve for 1 year if the patient meets the following criteria (i, ii, and iii):
     Note: Patients who have received < 1 year of therapy or those who are restarting therapy with Palynziq should be considered under criterion 1 (Phenylketonuria – Initial Therapy).

i. The patient is ≥ 18 years of age; AND

ii. The patient meets one of the following (a or b):

a) The patient's blood phenylalanine concentration is ≤ 600 micromol/L; OR

b) The patient has achieved a ≥ 20% reduction in blood phenylalanine concentration from pre-treatment baseline (i.e., blood phenylalanine concentration before starting Palynziq therapy); AND

iii. The patient is not receiving concomitant therapy with sapropterin dihydrochloride (Kuvan).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Palynziq has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

13. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	New criteria	05/30/2018
Annual revision	No criteria changes	05/15/2019
Annual revision	**Phenylketonuria – Initial Therapy:** The phrase "in adults" was removed from the approval condition; instead, a criterion was added to verify that the patient is ≥ 18 years of age. Examples of prior treatment modalities were moved to a note. **Phenylketonuria – Patients Continuing Therapy:** The phrase "in adults" was removed from the approval condition and moved into criteria as ≥ 18 years of age. Additionally, "[Maintenance therapy]" was removed from the approval condition; this is not needed. A note was added that patients who have received less than 1 year of Palynziq or who are restarting Palynziq should refer to Initial Therapy criteria. A criterion was added that concomitant use of Kuvan is not permitted (previously this was addressed under Conditions Not Recommended for Approval). **Concomitant Therapy with Palynziq and Kuvan:** Removed from policy. This is now addressed in criteria under the approval condition of "Phenylketonuia – Patients Continuing Therapy".	06/17/2020

PRIOR AUTHORIZATION POLICY

POLICY: Pheochromocytoma – Metyrosine Capsules and Phenoxybenzamine Capsules Prior Authorization Policy

- Metyrosine Capsules (Demser®, generics – Bausch Health, generics)

- Phenoxybenzamine capsules (Dibenzyline® – Concordia Pharmaceuticals, generics)

REVIEW DATE: 09/09/2020

OVERVIEW

Metyrosine capsules, a tyrosine hydroxylate inhibitor, is indicated for the treatment of patients with pheochromocytoma for:[1]

- **Preoperative preparation of patients for surgery**.
- **Management of patients when surgery is contraindicated**.
- **Chronic treatment of patients with malignant pheochromocytoma**.

Phenoxybenzamine capsules, a long-acting, adrenergic, alpha-receptor blocking agent, is indicated for the treatment of pheochromocytoma to control episodes of hypertension and sweating. If tachycardia is excessive, it may be necessary to use a beta-blocking agent concomitantly.[2]

Guidelines

A clinical practice guideline was published in 2014 from the Endocrine Society regarding from pheochromocytoma and paraganglioma.[3] The guidelines recommend preoperative alpha$_1$-adrenergic receptor blockers as the first choice to control blood pressure and prevent a hypertensive crisis. Both selective and non-selective alpha-blockers have been used (e.g., phenoxybenzamine, doxazosin, prazosin, and terazosin). Calcium channel blockers are the most often used add-on drug class to further improve blood pressure control in patients already treated with alpha-adrenergic receptor blockers. Preoperative co-administration of beta-adrenergic receptor blockers (e.g., atenolol, metoprolol, and propranolol) is utilized to control tachycardia after administration of alpha-adrenergic receptor blockers. Demser may be used in combination with alpha-adrenergic receptor blockers for a short period before surgery to further stabilize blood pressure to reduce blood loss and volume depletion during surgery.

The National Comprehensive Cancer Network (NCCN) guidelines for Neuroendocrine and Adrenal Tumors (version 2.2020 – July 24, 2020) address pheochromocytoma and paragangliomas.[4] Alpha blockade (e.g., terazosin, doxazosin, and prazosin) is recommended first-line for all hormonally-secreting pheochromocytomas and paragangliomas. After alpha blockade, if additional blood pressure support is required, the additional of dihydropyridine calcium channel blockers can be considered. Metyrosine can be used in addition to alpha blockage to stabilize blood pressure.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of metyrosine and phenoxybenzamine. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with metyrosine and phenoxybenzamine as well as the monitoring required for adverse events and long-term efficacy, approval requires metyrosine and phenoxybenzamine to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

Documentation: Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, and prescription receipts.

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indications

I. Coverage of phenoxybenzamine is recommended in those who meet the following criteria:

3. Pheochromocytoma. Approve phenoxybenzamine for 1 year if the patient meets the following criteria (A and B):

H) If brand Dibenzyline is requested, patient has tried AND cannot take generic phenoxybenzamine due to a formulation difference in the inactive ingredient(s) (e.g., difference in dyes, fillers, preservatives) between the brand and the bioequivalent generic product which, according to the prescriber, would result in a significant allergy or a serious adverse reaction **[documentation required]**.

I) The medication is prescribed by, or in consultation with, an endocrinologist or a physician who specializes in the management of pheochromocytoma.

II. Coverage of metyrosine is recommended in those who meet the following criteria:

1. Pheochromocytoma. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) Initial therapy. Approve for 1 year if the patient meets all of the following criteria (i, ii, and iii):

i. Patient has tried a selective alpha blocker (e.g., doxazosin, terazosin or prazosin); AND

ii. Patient has tried phenoxybenzamine (brand or generic); AND

iii. The medication is prescribed by, or in consultation with, an endocrinologist or a physician who specializes in the management of pheochromocytoma.

B) Patient is currently receiving metyrosine or has received metyrosine in the past. Approve for 1 year if prescribed by, or in consultation with, an endocrinologist or a physician who specializes in the management of pheochromocytoma.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of metyrosine and phenoxybenzamine is not recommended in the following situations:

242. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	08/29/2018
Annual Revision	**1. Pheochromocytoma:** For phenoxybenamine, the wording in reference to the criteria that listed a reason for use of Brand over generic was changed to "per the prescribing physician" was changed to "per the prescriber".	08/28/2019
Annual Revision	Generic metyrosine was added to the policy to align with brand Demser.	09/09/2020

PRIOR AUTHORIZATION POLICY

POLICY: Proprotein Convertase Subtilisin Kexin Type 9 Inhibitors – Praluent Prior Authorization Policy

- Praluent® (alirocumab injection for subcutaneous use – sanofi-aventis/Regeneron)

REVIEW DATE: 06/10/2020

OVERVIEW

Praluent, a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor antibody, is indicated for the following uses:[1]

- **Established cardiovascular (CV) disease**, in adults to reduce the risk of myocardial infarction (MI), stroke, and unstable angina requiring hospitalization.
- **Primary hyperlipidemia** (including **heterozygous familial hypercholesterolemia [HeFH]**), in adults as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe) to reduce low-density lipoprotein cholesterol (LDL-C).

The safety and efficacy of Praluent in children have not been established.[1] Repatha® (evolocumab injection for subcutaneous use) is another PCSK9 inhibitor that carries similar indications to Praluent.[2] Repatha is also indicated as an adjunct to diet and other low-density lipoprotein (LDL) therapies (e.g., statins ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

Guidelines

Many guidelines are available regarding the treatment of patients with dyslipidemia.[3-9] For patients with elevated LDL-C, statins are the cornerstone of therapy and recommended first-line to be used at maximally tolerated doses due to the established benefits regarding the reduction of CV risks. Atorvastatin 40 mg to

80 mg once daily (QD) and rosuvastatin 20 mg to 40 mg QD are considered high-intensity statins as they achieve LDL-C lowering of ≥ 50%. The American Heart Association/American College of Cardiology guidelines on the management of blood cholesterol (2018) defines atherosclerotic cardiovascular disease (ACSVD) as acute coronary syndrome (ACS), those with a history of MI, stable or unstable angina or coronary or other revascularizations, stroke, transient ischemic attack (TIA), or peripheral arterial disease (PAD).[3,4] Although LDL-C thresholds are not always recognized, in general, an LDL-C < 70 mg/dL is recommended for most patients with ASCVD to reduce CV risk. Use of a PCSK9 as an adjunct is justified if this goal is not met with maximally tolerated statins. Additionally, guidelines and reviews have recognized that patients with a coronary artery calcium or calcification score ≥ 300 Agatston units are at an increased risk of CV events.[10-13]

The National Lipid Association (NLA) published guidelines for the screening, diagnosis, and management of pediatric and adult patients with familial hypercholesterolemia (2011).[14] Familial hypercholesterolemia encompasses a group of genetic defects that cause severe elevations in LDL-C levels, as well as other lipid parameters. HeFH occurs in approximately 1 in 300 to 500 patients and is present in childhood. Total cholesterol (total-C) levels in HeFH range from 350 to 550 mg/dL, which can result in premature ASCVD. Aggressive lipid-lowering therapy is recommended to achieve LDL-C reductions of at least 50%. Both children and adults with LDL-C levels ≥ 190 mg/dL following lifestyle modifications will require medication therapy. Statins are the initial treatment for all adults with familial hypercholesterolemia. High or moderate intensity statins are recommended; low potency statins are generally inadequate for patients with familial hypercholesterolemia due to the markedly elevated LDL-C levels. In the pivotal trials for Praluent, HeFH was diagnosed utilizing Simon Broome criteria or Dutch Lipid Clinical Network criteria.[1] In an AHA scientific statement, it describes the Dutch Lipid Clinical Network Criteria and states that a score of > 5 on the scale makes the diagnosis of familial hypercholesterolemia highly probable.[15] Also, genetic testing can reveal a diagnosis of HeFH and clinical manifestations (e.g., tendon xanthomata) are highly suggestive of the condition.[15,16] Also, patients with an untreated LDL-C ≥ 190 mg/dL suggest familial hypercholesterolemia. In general, for patients with HeFH who have not yet manifested ASCVD, LDL-C levels ≤ 100 mg/dL are recommended. The addition of a PCSK9 inhibitor to statin therapy can be considered if this goal is not achieved.

In 2019 the AHA issued a scientific statement regarding statin safety and associated adverse events.[17] In general, statins are well-tolerated agents that have successfully led to decreased LDL-C levels which reduce CV events (e.g., MI, ischemic stroke). The risk of serious statin-induced muscle injury (e.g., rhabdomyolysis) is low (< 0.01%). In US clinical practice, about 10% of patients stop taking statin therapy due to subjective complaints, of which muscle symptoms without significantly raised creatine kinase levels are noted. Data suggest that the muscle symptoms that occur among patients are not caused by the pharmacologic effects of the statin and restarting statin therapy for these patients is important, especially among patients at high risk of CV events, for whom CV event prevention is important. Several studies have shown that patients believed that they were "statin intolerant". However, many patients were able to subsequently tolerate a statin upon rechallenge and receive the benefits provided with these agents. Other data support this occurrence.[18-20]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Praluent. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and monitoring of this new therapy, approval requires Praluent to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: None required.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Praluent is recommended in those who meet the following criteria:

FDA-Approved Indications

~~76.~~73. **Atherosclerotic Cardiovascular Disease (ASCVD) [Clinical].*** Approve for 3 years if the patient meets the following criteria (A, B, C, and D):

G) Patient is ≥ 18 years of age; AND

H) Patient has had one of the following conditions or diagnoses (i, ii, iii, iv, or v):

- **i.** A previous myocardial infarction (MI) or a history of an acute coronary syndrome (ACS); OR
- **ii.** Angina (stable or unstable); OR
- **iii.** A past history of stroke or transient ischemic attack (TIA); OR
- **iv.** Peripheral arterial disease (PAD); OR
- **v.** Patient has undergone a coronary or other arterial revascularization procedure in the past; AND
  Note: Examples include coronary artery bypass graft (CABG) surgery, percutaneous coronary intervention (PCI), angioplasty, and coronary stent procedures.

I) Patient meets one of the following criteria (i or ii):

- **i.** Patient meets both of the following (a and b):
  - **a)** Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 weeks; AND
  - **b)** Low-density lipoprotein cholesterol (LDL-C) level after this treatment remains ≥ 70 mg/dL; OR
- **ii.** Patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):
  - **a)** Patient experienced statin-related rhabdomyolysis; OR
    Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase (CK) levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]).
  - **b)** Patient meets all of the following [(1), (2), and (3)]:
    - **(1)** Patient experienced skeletal-related muscle symptoms; AND
      Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).
    - **(2)** The skeletal-related muscle symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND
    - **(3)** When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND

J) Medication is prescribed by, or in consultation with, a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders.

~~77.~~74. **Heterozygous Familial Hypercholesterolemia [HeFH].*** Approve for 3 years if the patient meets the following criteria (A, B, C, and D):

33. Patient is ≥ 18 years of age; AND

34. Patient meets one of the following criteria (i, ii, iii, iv, or v):

i. Patient has an untreated low-density lipoprotein cholesterol (LDL-C) level ≥ 190 mg/dL (prior to treatment with antihyperlipidemic agents); OR

ii. Patient has genetic confirmation of HeFH by mutations in the low-density lipoprotein receptor (LDLR), apolipoprotein B (APOB), proprotein convertase subtilisin kexin type 9 (PCSK9) or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene; OR

iii. Patient has been diagnosed with HeFH meeting one of the following diagnostic criteria thresholds (a or b):

a) Patient meets both of the following [(1) and (2)]:

(1) Prescriber used the Dutch Lipid Network criteria to diagnose HeFH; AND

(2) Patient has a score > 5; OR

b) Patient meets both of the following [(1) and (2)]:

(1) Prescriber used the Simon Broome criteria to diagnose HeFH; AND

(2) Patient met the threshold for "definite" or "possible" familial hypercholesterolemia; OR

iv. Patient has a treated low-density lipoprotein cholesterol (LDL-C) level ≥ 100 mg/dL (after treatment with antihyperlipidemic agents but prior to PCSK9 inhibitor therapy such as Praluent [alirocumab injection for subcutaneous use] or Repatha [evolocumab injection for subcutaneous use]); OR

v. Patient has clinical manifestations of HeFH; AND

Note: Examples of clinical manifestations of HeFH include cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma.

35. Patient meets one of the following criteria (i or ii):

i. Patient meets both of the following criteria (a and b):

a) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND

b) Low-density lipoprotein cholesterol (LDL-C) level after this treatment remains ≥ 70 mg/dL; OR

ii. Patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):

a) Patient experienced statin-related rhabdomyolysis; OR

Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase (CK) levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]);

b) Patient meets all of the following [(1), (2), and (3)]:

(1) Patient experienced skeletal-related muscle symptoms; AND

Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

(2) The skeletal-related muscle symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND

(3) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND

36. Medication is prescribed by, or in consultation with, a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders.

~~78.~~75. Primary Hyperlipidemia.* Approve for 3 years if the patient meets the following criteria (A, B, C, and D):

Note: This is not associated with atherosclerotic cardiovascular disease (ASCVD) or heterozygous familial hypercholesterolemia (HeFH) and may be referred to as combined hyperlipidemia, hypercholesterolemia (pure, primary), dyslipidemia, or increased/elevated low-density lipoprotein cholesterol (LDL-C) levels.

A) Patient is ≥ 18 years of age; AND

B) Patient has a coronary artery calcium or calcification (CAC) score ≥ 300 Agatston units; AND

C) Patient meets one of the following criteria (i or ii):

- **i.** Patient meets all of the following criteria (a, b and c):
  - **a)** Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]); AND
  - **b)** Patient has tried the one high-intensity statin therapy above along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND
  - **c)** Low-density lipoprotein cholesterol (LDL-C) level after this treatment regimen remains ≥ 100 mg/dL; OR
- **ii.** Patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):
  - **a)** Patient experienced statin-related rhabdomyolysis; OR
    Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase (CK) levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]).
  - **b)** Patient meets all of the following [(1), (2), and (3)]:
    - **(1)** Patient experienced skeletal-related muscle symptoms; AND
      Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness or tenderness).
    - **(2)** The skeletal-related muscle symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity combination product); AND
    - **(3)** When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms (e.g., myopathy, myalgia) resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND

D) Medication is prescribed by, or in consultation with, a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders.

Note:

* Patients may have a diagnoses that pertain to more than one FDA-approved indication, therefore, consider review under different approval conditions, if applicable. (e.g., patients with HeFH have had a clinical ASCVD event, patients with primary hyperlipidemia may have HeFH).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Praluent is not recommended in the following situations:

293. **Concurrent use of Praluent with Repatha® (evolocumab injection for SC use) or Juxtapid® (lomitapide capsules).** Repatha is another PCSK9 inhibitor and should not be used with Praluent.[2] Juxtapid, a microsomal triglyceride transfer protein inhibitor, is indicated as an adjunct to lipid-lowering medications and diet to modify lipid parameters (e.g., reduce LDL-C levels) in patients with

homozygous familial hypercholesterolemia (HoFH).[21] The efficacy and safety of Repatha or Juxtapid in combination with Praluent have not been established.

294. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date

Early Annual Revision	Documentation removed from the Policy that was set to be effective on 7/1/2018.	05/16/2018
Annual Revision	1. **Primary Hyperlipidemia** (not associated with ASCVD, HeFH, or Homozygous Familial Hypercholesterolemia): This new FDA-approved indication was added as an approval for a 3-years duration in patients ≥ 18 years of age who meet several other required criteria. See policy for details. 2. **Conditions Not Recommended for Approval**: Kynamro was removed from the list of agents in which Praluent should not be used with concomitantly because this product is no longer available.	06/12/2019
Annual Revision	The following changes were made: 1. **ASCVD:** Examples of coronary or other arterial revascularization procedures were removed from the criteria and placed in a note. Regarding the definition of rhabdomyolysis, the word "usually" was removed from the explanation associated with markedly elevated CK levels. Examples of skeletal-related muscle symptoms were removed from the criteria and placed in a note. 2. **HeFH:** Examples of clinical manifestations of HeFH were removed from the criteria and placed in a note. Regarding the definition of rhabdomyolysis, the word "usually" was removed from the explanation associated with markedly elevated CK levels. Examples of skeletal-related muscle symptoms were moved from the criteria to a note. 3. **Primary Hyperlipidemia:** The parameters surrounding the definition of primary hyperlipidemia were removed from the indication and placed in a note. Regarding the definition of rhabdomyolysis, the word "usually" was removed from the explanation associated with markedly elevated CK levels. Examples of skeletal-related muscle symptoms were removed from the criteria and placed in a note. Wording was clarified regarding the therapy requirement that the patient must try a high-intensity statin along with ezetimibe for 8 continuous weeks.	06/10/2020

ASCVD – Atherosclerotic cardiovascular disease; LDL-C – Low-density lipoprotein cholesterol; PCSK9 – Proprotein convertase subtilisin kexin type 9; HeFH – Heterozygous familial hypercholesterolemia; FDA – Food and Drug Administration; CK – Creatine kinase.

APPENDIX A.

Simon Broome Register Diagnostic Criteria.[15]

Definite Familial Hypercholesterolemia
Raised cholesterol
--Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years; OR
--Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult (aged > 16 years);
AND
--Tendon xanthomas in the patient or in a first (parent, sibling, or child) or second-degree relative (grandparent, aunt, or uncle);
OR
DNA-based evidence of LDL-receptor, familial defective APOB, or PCSK9 mutation.
Possible Familial Hypercholesterolemia
Raised cholesterol
--Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years; OR
--Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult (aged > 16 years);
AND
Family history of premature myocardial infarction younger than 50 years of age in second-degree relative or younger than 60 years of age in first-degree relative;
OR
Raised cholesterol
--Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years; OR
--Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult (aged > 16 years);
AND
Family history of raised cholesterol > 7.5 mmol (290 mg/dL) in adult first-degree or second-degree relative or > 6.7 mmol/L (260 mg/dL) in child or sibling aged < 16 years.

LDL-C – Low-density lipoprotein cholesterol; LDL – Low-density lipoprotein; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

APPENDIX B.

Dutch Lipid Network Criteria for Familial Hypercholesterolemia.[16]

Criteria	Score
Family History	
First-degree relative with known premature coronary and/or vascular disease (men < 55 years, women < 60 years)	1
First degree relative with known LDL-C > 95th percentile for age and sex	1
First-degree relative with tendon xanthomata and/or arcus cornealis, OR	2
Children aged < 18 years with LDL-C > 95th percentile for age and sex	2
Clinical History	
Patient with premature CAD (age as above)	2
Patient with premature cerebral or peripheral vascular disease (age as above)	1
Physical Examination	
Tendon xanthomas	6
Arcus cornealis at age < 45 years	4
LDL-C	
LDL-C ≥ 8.5 mmol/L (330 mg/dL)	8
LDL-C 6.5 to 8.4 mmol/L (250 to 329 mg/dL)	5
LDL-C 5.0 to 6.4 mmol/L (190 to 249 mg/dL)	3
LDL-C 4.0 to 4.9 mg/dL (155 to 189 mg/dL)	1
DNA analysis	
Functional mutation LDLR, APOB or PCSK9 gene	8
Stratification	**Total score**
Definite familial hypercholesterolemia	> 8
Probable familial hypercholesterolemia	6 to 8
Possible familial hypercholesterolemia	3 to 5
Unlikely familial hypercholesterolemia	< 3

LDL-C – Low-density lipoprotein cholesterol; CAD – Coronary artery disease; LDLR – Low-density lipoprotein receptor; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

PRIOR AUTHORIZATION POLICY

POLICY: Proprotein Convertase Subtilisin Kexin Type 9 Inhibitors – Repatha Prior Authorization Policy

- Repatha® (evolocumab injection for subcutaneous use [single-use prefilled syringes and Pushtronex™ system] – Amgen)

REVIEW DATE: 06/10/2020

OVERVIEW

Repatha, a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor antibody, is indicated for the following uses:[1]

- **Established cardiovascular (CV) disease**, in adults to reduce the risk of myocardial infarction (MI), stroke, and coronary revascularization.
- **Primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH]),** in adults as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe) to reduce low-density lipoprotein cholesterol (LDL-C).
- **Homozygous familial hypercholesterolemia (HoFH),** as an adjunct to diet and other low-density lipoprotein (LDL)-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) **in patients** who require additional lowering of LDL-C.

The safety and effectiveness of Repatha have not been established in pediatric patients with primary hyperlipidemia or HeFH. The safety and effectiveness of Repatha have not been established in pediatric patients with HoFH aged < 13 years.[1] Another PCSK9 inhibitor that is available is Praluent® (alirocumab injection for subcutaneous use).[2]

Guidelines

Many guidelines are available regarding the treatment of patients with dyslipidemia.[3-10] For patients with elevated LDL-C, statins are the cornerstone of therapy and recommended first-line to be used at maximally tolerated doses due to the established benefits regarding the reduction of CV risks. Atorvastatin 40 mg to 80 mg once daily (QD) and rosuvastatin 20 mg to 40 mg QD are considered high-intensity statins as they achieve LDL-C lowering of ≥ 50%. The American Heart Association/American College of Cardiology guidelines on the management of blood cholesterol (2018) defines atherosclerotic cardiovascular disease (ASCVD) as an acute coronary syndrome (ACS), those with a history of MI, stable or unstable angina or coronary or other revascularizations, stroke, transient ischemic attack (TIA), or peripheral arterial disease (PAD).[10] Although LDL-C thresholds are not always recognized, in general, an LDL-C < 70 mg/dL is recommended for most patients with ASCVD to reduce CV risk. Use of a PCSK9 as an adjunct is justified if this goal is not met with maximally tolerated statins.[10] Additionally, guidelines and reviews have recognized that patients with a coronary artery calcium or calcification score ≥ 300 Agatston units are at an increased risk of CV events.[10-13]

The National Lipid Association (NLA) published guidelines for the screening, diagnosis, and management of pediatric and adult patients with familial hypercholesterolemia (2011).[14] Familial hypercholesterolemia encompasses a group of genetic defects that cause severe elevations in LDL-C levels, as well as other lipid parameters. HeFH occurs in approximately 1 in 300 to 500 patients and is present in childhood. Total cholesterol (total-C) levels in HeFH range from 350 to 550 mg/dL, which can result in premature ASCVD. Aggressive lipid-lowering therapy is recommended to achieve LDL-C reductions of at least 50%. Both children and adults with LDL-C levels ≥ 190 mg/dL following lifestyle modifications will require medication therapy. Statins are the initial treatment for all adults with familial hypercholesterolemia. High or moderate intensity statins are recommended; low potency statins are generally inadequate for patients with familial hypercholesterolemia due to the markedly elevated LDL-C levels. In the pivotal trials for Praluent, HeFH was diagnosed utilizing Simon Broome criteria or Dutch Lipid Clinical Network criteria.[1] In an AHA scientific statement, it describes the Dutch Lipid Clinical Network Criteria and states that a score of > 5 on the scale makes the diagnosis of familial hypercholesterolemia highly probable.[15] Also, genetic testing can reveal a diagnosis of HeFH and clinical manifestations (e.g., tendon xanthomata) are highly suggestive of the condition. Also, patients with an untreated LDL-C ≥ 190 mg/dL suggest familial hypercholesterolemia.[15-17] In general, for patients with HeFH who have not yet manifested ASCVD, LDL-C levels ≤ 100 mg/dL are recommended. The addition of a PCSK9 inhibitor to statin therapy can be considered if this goal is not achieved.

In 2019 the AHA issued a scientific statement regarding statin safety and associated adverse events.[18] In general, statins are well-tolerated agents that have successfully led to decreased LDL-C levels which reduce CV events (e.g., MI, ischemic stroke). The risk of serious statin-induced muscle injury (e.g., rhabdomyolysis) is low (< 0.01%). In US clinical practice, about 10% of patients stop taking statin therapy due to subjective complaints, of which muscle symptoms without significantly raised creatine kinase levels are noted. Data suggests that the muscle symptoms that occur among patients are not caused by the pharmacologic effects of the statin and restarting statin therapy for these patients is important, especially among patients at high risk of CV events, for whom CV event prevention is important. Several studies have shown that patients believed that they were "statin intolerant". However, many patients were able to subsequently tolerate a statin upon rechallenge and receive the benefits provided with these agents. Other data support this occurrence.[19,20]

The 2014 HoFH position paper from the Consensus Panel on familial hypercholesterolemia of the European Atherosclerosis Society states the diagnosis of HoFH is made based on genetic or clinical criteria.[17] A definitive diagnosis can be made by genetic confirmation of two mutant alleles at the low density lipoprotein receptor, apolipoprotein B, PCSK9, or low-density lipoprotein receptor adaptor protein 1 gene locus. However, in some patients genetic confirmation remains elusive. Historically, HoFH has been commonly diagnosed based on LDL-C levels such as an untreated LDL-C > 500 mg/dL, or a treated LDL-C ≥ 300 mg/dL. Also confirming the diagnosis is the presence of xanthomas (cutaneous or tendinous) before the age of 10 years or a family history of elevated LDL-C levels consistent with HeFH in both parents.[17] Other clinical manifestations of HoFH include arcus cornea or xanthelasma.[14,17]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Repatha. All approvals are provided for the duration noted below. Due to the specialized skills required for evaluation and monitoring of this new therapy, approval requires Repatha to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: None required.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Repatha is recommended in those who meet the following criteria:

FDA-Approved Indications

~~79.~~76. **Atherosclerotic Cardiovascular Disease (ASCVD) [Clinical].*** Approve for 3 years if the patient meets the following criteria (A, B, C, and D):

K) Patient is ≥ 18 years of age; AND

L) Patient has had one of the following conditions or diagnoses (i, ii, iii, iv or v):

- **i.** A previous myocardial infarction (MI) or has a history of an acute coronary syndrome (ACS); OR
- **ii.** Angina (stable or unstable); OR
- **iii.** A past history of stroke or transient ischemic attack (TIA); OR
- **iv.** Peripheral arterial disease (PAD); OR
- **v.** Patient has undergone a coronary or other arterial revascularization procedure in the past; AND
  Note: Examples include coronary artery bypass graft (CABG) surgery, percutaneous coronary intervention (PCI), angioplasty, and coronary stent procedures.

M) Patient meets one of the following criteria (i or ii):

- **i.** Patient meets both of the following (a and b):
  - **a)** Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin tablets ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND
  - **b)** Low-density lipoprotein cholesterol (LDL-C) level after this treatment remains ≥ 70 mg/dL; OR
- **ii.** Patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):
  - **a)** Patient experienced statin-related rhabdomyolysis; OR
    Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase (CK) levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury

(noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]); OR

b) Patient meets all of the following [(1), (2), and (3)]:

(1) Patient experienced skeletal-related muscle symptoms; AND

(2) Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

(3) The skeletal-related muscle symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND

(4) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND

N) Medication is prescribed by, or in consultation with, a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders.

~~80.~~77. **Heterozygous Familial Hypercholesterolemia (HeFH).*** Approve for 3 years if the patient meets the following criteria (A, B, C, and D):

37. Patient is ≥ 18 years of age; AND

38. Patient meets one of the following criteria (i, ii, iii, iv or v):

i. Patient has an untreated low-density lipoprotein cholesterol (LDL-C) ≥ 190 mg/dL (prior to treatment with antihyperlipidemic agents); OR

ii. Patient has genetic confirmation of HeFH by mutations in the low-density lipoprotein receptor (LDLR), apolipoprotein B (APOB), proprotein convertase subtilisin kexin type 9 (PCSK9) or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene; OR

iii. Patient has been diagnosed with HeFH meeting one of the following diagnostic criteria thresholds (a or b):

a) Patient meets both of the following [(1) and (2)]:

(1) Prescriber used the Dutch Lipid Network criteria to diagnose HeFH; AND

(2) Patient had a score> 5; OR

b) Patient meets both of the following [(1) and (2)]:

(1) Prescriber used the Simon Broome criteria to diagnose HeFH; AND

(2) Patient met the threshold for "definite" or "possible" familial hypercholesterolemia; OR

iv. Patient has a treated low-density lipoprotein cholesterol (LDL-C) level ≥ 100 mg/dL (after treatment with antihyperlipidemic agents but prior to PCSK9 inhibitor therapy such as Praluent® [alirocumab injection for SC use] or Repatha); OR

v. Patient has clinical manifestations of HeFH; AND

Note: Examples of clinical manifestations of HeFH include cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma.

39. Patient meets one of the following criteria (i or ii):

i. Patient meets both of the following criteria (a and b):

~~**a)**~~ Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin tablets ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND

~~**b)**~~ Low-density lipoprotein cholesterol (LDL-C) level after this treatment remains ≥ 70 mg/dL; OR

ii. Patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):

a) Patient experienced statin-related rhabdomyolysis; OR

Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase (CK) levels (at least 10 times the upper limit of normal),

along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]); OR

b) Patient meets all of the following [(1), (2), and (3)]:

(1) Patient experienced skeletal-related muscle symptoms; AND
Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

(2) The skeletal-related muscle symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND

(3) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND

40. Medication is prescribed by, or in consultation with, a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders.

~~81.~~78. Homozygous Familial Hypercholesterolemia (HoFH).* Approve for 3 years if the patient meets the following criteria (A, B, C, and D):

A) Patient is ≥ 13 years of age; AND

B) Patient meets one of the following (i, ii, iii or iv):

i. Patient has genetic confirmation of two mutant alleles at the low-density lipoprotein receptor (LDLR), apolipoprotein B (APOB), proprotein convertase subtilisin kexin type 9 (PCSK9) or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene locus; OR

ii. Patient has an untreated low-density lipoprotein (LDL-C) level > 500 mg/dL (prior to treatment with antihyperlipidemic agents); OR

iii. Patient has a treated low-density lipoprotein cholesterol (LDL-C) level ≥ 300 mg/dL (after treatment with antihyperlipidemic agents but prior to agents such as Repatha or Juxtapid® [lomitapide capsules]); OR

iv. Patient has clinical manifestations of HoFH; AND
Note: Examples of clinical manifestation of HoFH include cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma.

C) Patient meets one of the following criteria (i or ii):

i. Patient meets both of the following (a and b):

a) Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND

b) Low-density lipoprotein cholesterol (LDL-C) level after this treatment remains ≥ 70 mg/dL; OR

ii. Patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):

a) Patient experienced statin-related rhabdomyolysis; OR
Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase (CK) levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]); OR

b) Patient meets all of the following criteria [(1), (2), and (3)]:

(1) Patient experienced skeletal-related muscle symptoms; AND
Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

(2) The skeletal-related muscle symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND

(3) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND

D) Medication is prescribed by, or in consultation with, a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders.

~~82.~~79. **Primary Hyperlipidemia.*** Approve for 3 years if the patient meets the following criteria (A, B, C, and D):

Note: This is not associated with atherosclerotic cardiovascular disease (ASCVD), heterozygous familial hypercholesterolemia (HeFH), or homozygous familial hypercholesterolemia (HoFH) and may be referred to as combined hyperlipidemia, hypercholesterolemia (pure, primary), dyslipidemia, or increased/elevated low-density lipoprotein cholesterol (LDL-C) levels.

E) Patient is ≥ 18 years of age; AND

F) Patient has a coronary artery calcium or calcification (CAC) score ≥ 300 Agatston units; AND

G) Patient meets one of the following criteria (i or ii):

i. Patient meets all of the following criteria (a, b, and c):

~~**a)**~~ Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin tablets ≥ 20 mg daily [as a single-entity or as a combination product]); AND

~~**b)**~~ Patient has tried one high-intensity statin therapy above along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND

~~**c)**~~ Low-density lipoprotein cholesterol (LDL-C) level after this treatment regimen remains ≥ 100 mg/dL; OR

ii. Patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):

a) Patient experienced statin-related rhabdomyolysis; OR

Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase (CK) levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]); OR

b) Patient meets all of the following [(1), (2), and (3)]:

(1) Patient experienced skeletal-related muscle symptoms; AND

Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).

(2) The skeletal-related muscle symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND

(3) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND

H) Medication is prescribed by, or in consultation with, a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders.

Note:

* Patients may have a diagnoses that pertain to more than one FDA-approved indication, therefore, consider review under different approval conditions, if applicable (e.g., patients with HeFH have had a clinical ASCVD event, patients with primary hyperlipidemia may have HeFH).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Repatha is not recommended in the following situations:

295. Concurrent use of Repatha with Praluent® (alirocumab injection for subcutaneous use use) or Juxtapid (lomitapide capsules). Praluent is another PCSK9 inhibitor and should not be used with Repatha.[2] Juxtapid, a microsomal triglyceride transfer protein inhibitor, is indicated as an adjunct to lipid-lowering medications and diet to modify lipid parameters (e.g., reduce LDL-C levels) in patients with HoFH.[21] The efficacy and safety of using Praluent or Juxtapid in combination with Repatha have not been established.

296. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	Documentation removed from the Policy that was set to be effective on 7/1/2018.	05/16/2018
Annual Revision	**Conditions Not Recommended for Approval:** Kynamro was removed from the list of agents in which Repatha should not be used with concomitantly because this product is no longer available.	06/12/2019
Annual Revision	The following changes were made: 1. **ASCVD:** Examples of coronary or other arterial revascularization procedures were removed from the criteria and placed in a note. Regarding the definition of rhabdomyolysis, the word "usually" was removed from the explanation associated with markedly elevated CK levels. Examples of skeletal-related muscle symptoms were removed from the criteria and placed in a note. 2. **HeFH:** Examples of clinical manifestations of HeFH were removed from the criteria and placed in a note. Regarding the definition of rhabdomyolysis, the word "usually" was removed from the explanation associated with markedly elevated CK levels. Examples of skeletal-related muscle symptoms were moved from the criteria to a note. 3. **HoFH:** Examples of clinical manifestations of HoFH were removed from the criteria and placed in a note. Regarding the definition of rhabdomyolysis, the word "usually" was removed from the explanation associated with markedly elevated CK levels. Examples of skeletal-related muscle symptoms were moved from the criteria to a note. 4. **Primary Hyperlipidemia:** The parameters surrounding the definition of primary hyperlipidemia were removed from the indication and placed in a note. Regarding the definition of rhabdomyolysis, the word "usually was removed from the explanation associated with markedly elevated CK levels. Examples of skeletal-related muscle symptoms were removed from the criteria and placed in a note. Wording was clarified regarding the therapy requirement that the patient must try a high-intensity statin along with ezetimibe for 8 continuous weeks.	06/10/2020

ASCVD – Atherosclerotic cardiovascular disease; LDL-C – Low-density lipoprotein cholesterol; PCSK9 – Proprotein convertase subtilisin kexin type 9; FDA – Food and Drug Administration; HeFH – Heterozygous familial hypercholesterolemia; HoFH – Homozygous familial hypercholesterolemia; CK – Creatine kinase.

APPENDIX A

Simon Broome Register Diagnostic Criteria.[15]

Definite Familial Hypercholesterolemia
Raised cholesterol
--Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years; OR
--Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult (aged > 16 years);
AND
--Tendon xanthomas in the patient or in a first (parent, sibling, or child) or second-degree relative (grandparent, aunt, or uncle);
OR
DNA-based evidence of LDL-receptor, familial defective APOB, or PCSK9 mutation.
Possible Familial Hypercholesterolemia
Raised cholesterol
--Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years; OR
--Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult (aged > 16 years);
AND
Family history of premature myocardial infarction younger than 50 years of age in second-degree relative or younger than 60 years of age in first-degree relative;
OR
Raised cholesterol
--Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years; OR
--Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult (aged > 16 years);
AND
Family history of raised cholesterol > 7.5 mmol (290 mg/dL) in adult first-degree or second-degree relative or > 6.7 mmol/L (260 mg/dL) in child or sibling aged < 16 years.

LDL-C – Low-density lipoprotein cholesterol; LDL – Low-density lipoprotein; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

APPENDIX B.

Dutch Lipid Network Criteria for Familial Hypercholesterolemia.[16]

Criteria	Score
Family History	
First-degree relative with known premature coronary and/or vascular disease (men < 55 years, women < 60 years)	1
First degree relative with known LDL-C > 95th percentile for age and sex	1
First-degree relative with tendon xanthomata and/or arcus cornealis, OR	2
Children aged < 18 years with LDL-C > 95th percentile for age and sex	2
Clinical History	
Patient with premature CAD (age as above)	2
Patient with premature cerebral or peripheral vascular disease (age as above)	1
Physical Examination	
Tendon xanthomas	6
Arcus cornealis at age < 45 years	4
LDL-C	
LDL-C ≥ 8.5 mmol/L (330 mg/dL)	8
LDL-C 6.5 to 8.4 mmol/L (250 to 329 mg/dL)	5
LDL-C 5.0 to 6.4 mmol/L (190 to 249 mg/dL)	3
LDL-C 4.0 to 4.9 mg/dL (155 to 189 mg/dL)	1
DNA analysis	
Functional mutation LDLR, APOB or PCSK9 gene	8
Stratification	**Total score**
Definite familial hypercholesterolemia	> 8
Probable familial hypercholesterolemia	6 to 8
Possible familial hypercholesterolemia	3 to 5
Unlikely familial hypercholesterolemia	< 3

LDL-C – Low-density lipoprotein cholesterol; CAD – Coronary artery disease; LDLR – Low-density lipoprotein receptor; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

PRIOR AUTHORIZATION POLICY

POLICY: Psychiatry – Spravato Prior Authorization Policy

- Spravato™ (esketamine nasal spray – Janssen)

REVIEW DATE: 03/25/2020; selected revision 08/05/2020 and 09/16/2020

OVERVIEW

Spravato, a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist, is indicated in conjunction with an oral antidepressant for the treatment of:[1]

- Depressive symptoms in adults with **major depressive disorder (MDD) with acute suicidal ideation or behavior**.
- **Treatment-resistant depression** (TRD) in adults.

Limitation of Use: The effectiveness of Spravato in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of Spravato does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of Spravato. Spravato is not approved as an anesthetic agent. The safety and effectiveness of Spravato as an anesthetic agent have not been established.

Spravato should be administered in conjunction with an oral antidepressant.[1] For MDD with acute suicidal ideation or behavior, the recommended dosage is 84 mg twice weekly for 4 weeks. The dosage may be reduced to 56 mg twice weekly based on tolerability. After 4 weeks of treatment, evidence of therapeutic benefit should be evaluated to determine need for continued treatment. The use of Spravato, in conjunction with an oral antidepressant, beyond 4 weeks has not been systematically evaluated in the treatment of depressive symptoms in patients with MDD with acute suicidal ideation or behavior. For treatment-resistant depression, the recommended dose is 56 mg intranasally

on Day 1, followed by 56 mg or 84 mg intranasally twice weekly for Weeks 1 to 4. On Weeks 5 to 8, Spravato should be administered once weekly at a dose of 56 mg or 84 mg intranasally. On Week 9 and thereafter, the dosing frequency should be individualized to the least frequent dosing to maintain remission/response (either every 2 weeks or once weekly) at a dose of 56 mg or 84 mg. Spravato must be administered under the direct supervision of a healthcare provider.

Disease Overview

Major depressive disorder is a serious, life-threatening condition with high rates of morbidity and a chronic disease course.[2] Major depressive disorder is considered the leading cause of disability worldwide and is also associated with increased mortality rates.[3,4] About 30% to 40% of patients with major depressive disorder fail to respond to first-line treatments including oral antidepressant medications of all classes (e.g., selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], tricyclic antidepressants [TCAs], bupropion) and/or psychotherapy.[2,5] In addition, the onset of treatment response for these modalities, even when effective, often takes ≥ 4 weeks, leading to greater suffering, expense, and risk. For regulatory purposes, the FDA considers patients to have treatment-resistant depression if they have MDD and they have not responded to treatment despite trials of at least two antidepressants given at adequate doses for an adequate duration in the current episode.[2]

The available treatments for treatment-resistant depression are limited.[2] Prior to the approval of Spravato, only one medication was FDA-approved for treatment-resistant depression, Symbyax® (olanzapine and fluoxetine capsules). Symbyax is indicated for treatment-resistant depression (major depressive disorder in patients who do not respond to two separate trials of different antidepressants of adequate dose and duration in the current episode) and acute depressive episodes in bipolar I disorder.[6]

Guidelines

According to the American Psychiatric Association practice guideline for the treatment of patients with major depressive disorder (2010), the effectiveness of antidepressants is generally comparable between classes and within classes.[7] Therefore, the initial selection of antidepressant will largely be based on the anticipated side effects, the safety or tolerability of these side effects for the individual patient, pharmacological properties of the medication (e.g., half-life, drug interactions), and additional factors such as medication response in prior episodes, cost, and patient preference. In patients with depression who either have not responded or have had trouble tolerating one SSRI agent, a trial of another SSRI (or another antidepressant) may be effective and/or better tolerated. Patients who have had a partial response to antidepressant monotherapy can be augmented with another antidepressant from a different pharmacological class or with another non-antidepressant medication, such as lithium, thyroid hormone, an anticonvulsant, a psychostimulant, or an atypical antipsychotic.

Abuse and Misuse

Spravato contains esketamine, a Schedule III controlled substance (CIII), which may be subject to abuse and diversion.[1] Assess each patient's risk for abuse or misuse prior to prescribing Spravato. All patients receiving Spravato should be monitored for the development of these behaviors or conditions, including drug-seeking behavior, while on therapy. Patients with a history of drug abuse or dependence are at greater risk. Careful consideration should be given prior to prescribing Spravato to individuals with a history of substance use disorder.

Safety

Spravato labeling includes a Boxed Warning regarding sedation, dissociation, abuse and misuse, and suicidal thoughts and behaviors in pediatric and young adult patients.[1] The most common psychological effects of Spravato were dissociative or perceptual changes (including distortion of time, space and illusions), derealization and depersonalization (61% to 84% of patients treated with Spravato developed dissociative or perceptual changes based on the Clinician-Administered Dissociative States Scale). Given its potential to induce dissociative effects, carefully assess patients with psychosis before administering Spravato; treatment should be initiated only if the benefit outweighs the risk.

Because of the risks of serious adverse outcomes resulting from sedation, dissociation, and abuse and misuse, Spravato is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).[1] Healthcare settings must be certified in the program and ensure that Spravato is only dispensed in healthcare settings and administered to patients who are enrolled in the program, administered by patients under the direct observation of a

healthcare provider, and that patients are monitored by a healthcare provider for at least 2 hours after administration of Spravato. Pharmacies must be certified in the REMS and must only dispense Spravato to healthcare settings that are certified in the program.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Spravato. Because of the specialized skills required for evaluation and diagnosis of patients treated with Spravato as well as the monitoring required for adverse events and efficacy, approval requires Spravato to be prescribed by a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Spravato is recommended in those who meet the following criteria:

FDA-Approved Indications

257. Major Depressive Disorder with Acute Suicidal Ideation or Behavior. Approve for 2 months if the patient meets the following criteria (A, B, C, D, and E):

A) Patient is ≥ 18 years of age; AND

B) Patient has major depressive disorder that is considered to be severe, according to the prescriber; AND

C) Patient is concomitantly receiving at least one oral antidepressant; AND
Note: Antidepressants may include, but are not limited to, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), mirtazapine, and bupropion.

D) Patient has one of the following (i or ii):
- **i.** No history of psychosis; OR
- **ii.** History of psychosis and the prescriber believes that the benefits of Spravato outweigh the risks; AND

E) The medication is prescribed by a psychiatrist.

258. Treatment-Resistant Depression. Approve for 6 months if the patient meets the following criteria (A, B, C, D, E, and F):

A) Patient is ≥ 18 years of age; AND

B) Patient meets both of the following (i and ii):
- **i.** Patient has demonstrated nonresponse (≤ 25% improvement in depression symptoms or scores) to at least two different antidepressants, each from a different pharmacologic class, according to the prescriber; AND

  Note: Different pharmacologic classes of antidepressants include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), bupropion, mirtazapine, etc.
- **ii.** Each antidepressant was used at therapeutic dosages for at least 6 weeks in the current episode of depression, according to the prescriber; AND

C) Patient is concomitantly receiving at least one oral antidepressant; AND
Note: Antidepressants may include, but are not limited to, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), mirtazapine, and bupropion.

D) Patient has one of the following (i or ii):
- **i.** No history of psychosis; OR

ii. History of psychosis and the prescriber believes that the benefits of Spravato outweigh the risks; AND

E) The patient's history of controlled substance prescriptions has been checked using the state prescription drug monitoring program (PDMP), unless unavailable in the state (see note below), according to the prescriber; AND

Note: As of 03/25/2020, the state of Missouri is the only state in the US that does not have a PDMP program in place.

F) The medication is prescribed by a psychiatrist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Spravato is not recommended in the following situations:

243. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	03/11/2019
Selected Revision	Addition of the following language to the criterion requiring trials of two different antidepressants: each from a different pharmacologic class (e.g., selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], tricyclic antidepressants [TCAs], bupropion, mirtazapine, etc.). No other changes to criteria.	03/20/2019
Annual Revision	No change to criteria.	03/25/2020
Selected Revision	Addition of criteria for a new indication for Acute Suicidal Ideation or Behavior in adults with major depressive disorder receiving at least one oral antidepressant. For the Treatment-Resistant Depression criteria, prescribing physician was changed to prescriber and examples of different pharmacologic classes of antidepressants were moved to a Note.	08/05/2020
Selected Revision	**Acute Suicidal Ideation or Behavior**: Approval condition was changed to "**Major Depressive Disorder with Acute Suicidal Ideation or Behavior**" and the criterion for "major depressive disorder" was modified to include "that is considered to be severe, according to the prescriber".	9/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Psychiatry – Zulresso™ (brexanolone injection for intravenous use – Sage Therapeutics)

DATE REVIEWED: 05/13/2020

OVERVIEW

Zulresso, a neuroactive steroid gamma-aminobutric acid (GABA) A receptor positive modulator, is indicated for the treatment of postpartum depression in adults.[1] Zulresso was approved under a priority review by the FDA and was granted a breakthrough therapy designation. The active ingredient of Zulpressa, brexanolone, is chemically identical to endogenous allopregnanolone. Plasma concentrations of allopregnanolone increase during pregnancy and decrease substantially after childbirth in both rodents and humans, and fluctuations in allopregnanolone have demonstrated effects on anxiety and depression in animal models.[2] The mechanism of action of Zulresso is not fully understood but it has been shown to modulate GABA-mediated currents from recombinant human $GABA_A$ receptors in mammalian cells expressing $\alpha_1\beta_2\gamma_2$, $\alpha_4\beta_3\delta$, and $\alpha_6\beta_3\delta$ receptor subunits.[1]

The efficacy of Zulresso was established in two Phase III, US-only, randomized, double-blind, placebo-controlled, multicenter, pivotal studies in patients with moderate to severe postpartum depression initiating treatment within 6 months of delivery.[2] Zulresso is administered as a one-time, continuous intravenous (IV) infusion over 60 hours.[1]

Disease Overview

Postpartum (or peripartum) depression is a major depressive episode with onset during pregnancy or within 4 weeks of delivery that can have serious effects on the maternal-infant bond and later infant development.[3] Postpartum depression is estimated to affect 10% to 20% of women who give birth worldwide and occurs in low- to high-income countries.[2] Approximately 40% to 80% of cases of postpartum depression are considered moderate to severe. In the US, the estimated prevalence of postpartum depression in new mothers varies by state from 8% to 20%, with an overall prevalence of approximately 12%.

Postpartum depression is symptomatically indistinguishable from major depression.[3] However, the timing of its onset has led to the acknowledgement of it potentially being a unique illness. As with other forms of depression, it is characterized by sadness and/or loss of interest in activities that one used to enjoy and a decreased ability to feel pleasure and may present with symptoms such as cognitive impairment, feelings of worthlessness or guilt, or suicidal ideation.[4] Because of the risk of suicide, postpartum depression is considered a life-threatening condition.[3]

Abuse and Misuse

Zulresso is a CIV controlled substance.[1] In a human abuse potential study, 3% of volunteers administered Zulresso 90 mcg/kg and 13% of volunteers administered Zulresso 270 mcg/kg (three times the maximum recommended infusion rate) reported euphoric mood compared with no volunteers administered placebo over a 1 hour infusion.

Safety

Based on findings from animal studies of other drugs that enhance GABAergic inhibition, Zulresso may cause fetal harm.[1] Currently, there are no available data on Zulresso use in pregnant women to determine a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. A pregnancy exposure registry is available to monitor pregnancy outcomes in women exposed to antidepressants during pregnancy.

Zulresso has a Boxed Warning regarding excessive sedation and sudden loss of consciousness.[1] Because of the risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Patients must be accompanied during interactions with their children. During the infusion, patients must be monitored for sedative effects every 2 hours during planned, non-sleep periods. If there are signs or symptoms of excessive sedation, the infusion must be stopped immediately. After symptom resolution, the infusion may be restarted at the same or a lower dose.

Due to the risks of serious adverse events resulting from excessive sedation and sudden loss of consciousness, Zulresso is only available through a restricted distribution system under a REMS.[1,5] The Zulresso REMS requires healthcare facilities be enrolled in the program and ensure that Zulresso is only administered to patients enrolled in the program. Pharmacies are required to be certified and can only dispense Zulresso to certified healthcare facilities. Patients must enroll in the program prior to administration of Zulresso. The REMS requires the prescriber and the patient sign the Patient Enrollment Form that clearly states that the patient understands the risk of excessive sedation and loss of consciousness associated with Zulresso. A healthcare provider must be available on site to monitor the patient for the duration of the infusion. Patients must be monitored for hypoxia using continuous pulse oximetry and for excessive sedation every 2 hours during planned, non-sleep periods.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Zulresso. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zulresso as well as the monitoring required for adverse events and long-term efficacy, approval requires Zulresso to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Note that a 1-month (30 days) approval duration is applied to allow for the scheduling and administration of the one-time, 60-hour infusion of Zulresso.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zulresso is recommended in those who meet the following criteria:

FDA-Approved Indications

259. Postpartum Depression. Approve for 1 month if the patient meets the following criteria (A, B, C, D, and E):

- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has been diagnosed with moderate to severe depression; AND
- **C)** Patient is ≤ 6 months postpartum; AND
- **D)** Patient is not currently pregnant; AND
- **E)** Zulresso is being prescribed by, or in consultation with, a psychiatrist or an obstetrician-gynecologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Zulresso has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

244. Previous Treatment with Zulresso During the Current Episode of Postpartum Depression.

245. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	05/01/2019
Annual revision	No change to criteria.	05/13/2020

PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary – Corticosteroid/Long-Acting Beta$_2$-Agonist Combination Inhalers

- Advair Diskus® (fluticasone propionate/salmeterol inhalation powder – GlaxoSmithKline; generics [including Wixela™ Inhub™])
- Advair® HFA (fluticasone propionate/salmeterol inhalation aerosol – GlaxoSmithKline)
- AirDuo® Digihaler™ (fluticasone propionate/salmeterol inhalation powder – Teva)
- AirDuo® RespiClick® (fluticasone propionate/salmeterol inhalation powder – Teva; generic)
- Breo® Ellipta® (fluticasone furoate/vilanterol inhalation powder – GlaxoSmithKline)
- Dulera® (mometasone furoate/formoterol fumarate inhalation aerosol – Merck)
- Symbicort® (budesonide/formoterol fumarate inhalation aerosol – AstraZeneca; generic)

REVIEW DATE: 07/01/2020; selected revision 09/16/2020

OVERVIEW

Fluticasone propionate and salmeterol inhalation powder (Advair Diskus, generics [including Wixela Inhub]), Advair HFA, AirDuo Digihaler, AirDuo RespiClick (and authorized generic), Breo Ellipta, Dulera, and Symbicort (and authorized generic) are inhaled corticosteroid (ICS) and long-acting beta-agonist (LABA) combination products that exert local anti-inflammatory effects in the lungs and produce bronchial smooth muscle relaxation.[1-6] All of the corticosteroid/long-acting beta$_2$-agonist combination inhalers are indicated for the treatment of asthma.[1-6] Age indications vary by agent. Fluticasone propionate and salmeterol inhalation powder (Advair Diskus, generics [including Wixela Inhub]), Breo Ellipta, and Symbicort are also indicated for the maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive lung disease (COPD), including chronic bronchitis and/or emphysema.[1,3,5] Advair HFA and Dulera are not FDA-approved for the treatment of COPD; however, both products have been studied for this use.[2,4,7-9] The AirDuo products also have not specifically been studied in patients with COPD. However, these agents were filed as a New Drug Application under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.[6] This approval pathway relies in part upon evidence not developed by

the applicant. In the case of these agents, the literature and safety and effectiveness evidence supporting the approval and use of Advair Diskus (indicated in patients with COPD) are considered part of the evidence supporting the approval and use of the AirDuo products.

Guidelines

The 2020 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for the diagnosis, management, and prevention of COPD support the use of combination ICS/LABA therapy in select highly symptomatic patients who are at high risk for COPD exacerbations.[10] The 2020 Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention states that low-dose ICS/LABA combination therapy is the preferred treatment for adults and adolescents when low-dose ICS monotherapy fails to control the patient's asthma.[29] Certain low-dose ICS/LABA combinations (i.e., those containing formoterol) are also recommended as initial maintenance and reliever therapy for asthma as well. European Respiratory Society (ERS) guidelines on the diagnosis and treatment of chronic cough in adults and children recommend a short-term trial (2 to 4 weeks) of ICS and long-acting bronchodilator (e.g. a LABA) combination in adults with chronic cough and fixed airflow obstruction.[20]

Other Uses with Supportive Evidence

There are also data to support the use of ICS/LABA inhalers in patients with postinfectious cough. Subacute postinfectious cough may have multiple possible underlying etiologies, including asthma.[11,12] The underlying cause of the cough must be determined before making therapeutic decisions. In this situation, ICS/LABA combination therapy may be used as diagnostic empiric therapy in determining the cause of cough (i.e., rule out asthma). When a patient with subacute cough presents with wheezes, rhonchi, or crackles with a normal chest radiograph, it may be a reasonable option to consider therapy with an inhaled bronchodilator and ICS. If cough following an upper respiratory tract infection persists for > 8 weeks, diagnoses other than postinfectious cough should be considered.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of fluticasone propionate and salmeterol inhalation powder (Advair Diskus, generics [including Wixela Inhub]), Advair HFA, AirDuo Digihaler, AirDuo RespiClick, fluticasone and salmeterol inhalation powder (authorized generic of AirDuo RespiClick), Breo Ellipta, Dulera, Symbicort, and budesonide/formoterol fumarate inhalation aerosol (authorized generic of Symbicort). The purpose of this policy is to support the use of the corticosteroid/long-acting beta$_2$-agonist combination inhalers in chronic conditions where the products are indicated or their use is appropriate. All approvals are provided for the duration listed below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: Prescription claims (prior 130 days) for respiratory medications (e.g., leukotriene receptor antagonists; xanthines; inhaled mast cell stabilizers; oral and inhaled beta-agonists; inhaled corticosteroids, inhaled anticholinergic agents) are used as a surrogate marker for a diagnosis of asthma or chronic obstructive pulmonary disease (COPD). If use of these medications is not met at the point-of-service, coverage will be determined by prior authorization criteria. When available, the ICD-10 codes for asthma and COPD (including chronic bronchitis/emphysema) will also be used in automation to generate an approval of the requested medication (see Appendix A).

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of fluticasone propionate and salmeterol inhalation powder (Advair Diskus, generics [including Wixela Inhub]), Advair HFA, AirDuo Digihaler, AirDuo RespiClick, fluticasone and salmeterol inhalation powder (authorized generic of AirDuo RespiClick), Breo Ellipta, Dulera, Symbicort, or budesonide/formoterol fumarate inhalation aerosol (authorized generic of Symbicort) is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Asthma/Reactive Airway Disease.** Approve for 3 years.
2. **Chronic Obstructive Pulmonary Disease.** Approve for 3 years.
3. **Chronic Bronchitis.** Approve for 3 years.
4. **Emphysema.** Approve for 3 years.

Other Uses with Supportive Evidence

5. **Postinfectious Cough.** Approve for 2 months.
   Note: Postinfectious cough is cough that persists after an acute respiratory infection has resolved.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of fluticasone propionate and salmeterol inhalation powder (Advair Diskus, generics [including Wixela Inhub]), Advair HFA, AirDuo Digihaler, AirDuo RespiClick, fluticasone and salmeterol inhalation powder (authorized generic of AirDuo RespiClick), Breo Ellipta, Dulera, and Symbicort is not recommended in the following situations:

297. **Acute Cough Associated with the Common Cold.** Note: This includes symptoms associated with a current rhinovirus infection.
   There are no data to support the use of ICS/LABA combination therapy in treating this condition. American College of Chest Physicians (ACCP) guidelines for the treatment of acute cough associated with the common cold do not recommend using an ICS or a bronchodilator in treating this condition.[11,26] Over-the-counter (OTC) cough and cold preparations are recommended, as is honey in pediatric patients.

298. **Chronic Cough due to Gastroesophageal Reflux Disease (GERD).** There are no data to support the use of ICS/LABA combination therapy in treating this condition. The ACCP guidelines for the management of chronic cough due to GERD recommend treatment of the underlying condition and do not mention the use of any inhaled therapies.[13,24]

299. **Acute Cough due to an Acute Respiratory Infection.** Note: Examples of an acute respiratory infection are acute bronchitis, sinusitis, influenza, or pneumonia. An acute exacerbation of chronic bronchitis is not the same as acute bronchitis.
   ACCP guidelines for the management of acute cough due to acute bronchitis in immunocompetent adult outpatients do not recommend routine use of inhaled corticosteroids and inhaled beta-agonists.[14] Current evidence is not sufficient to prove that these therapies are safe and effective at reducing the severity and duration of cough in this setting. Bronchodilators are also not a recommended therapeutic option in treating cough associated with acute bacterial sinusitis.[12] Additional ACCP guidelines for the management of acute cough due to suspected pneumonia or influenza state that there is insufficient evidence on the use of nonantibiotic symptomatic therapies such as ICSs or bronchodilators.[26] There are no data to support the use of ICS/LABA combination therapy in treating these conditions.

300. **Chronic Cough due to Non-Asthmatic Eosinophilic Bronchitis (NAEB).** There are no data to support the use of ICS/LABA combination therapy in treating this condition. Per the guidelines for the management of chronic cough due to NAEB from ACCP ICSs are the recommended first-line treatment.[11,23] One of the clinical characteristics of NAEB is chronic cough without evidence of variable airflow obstruction or airway hyperresponsiveness. As a result, a beta-agonist bronchodilator would not be expected to be useful in treating this condition.

301. **Chronic Cough due to Bronchiolitis.** The ACCP guidelines do not recommend bronchodilators as a therapeutic option in treating bronchiolitis.[11,15] Use of asthma medications is discouraged unless other evidence of asthma is present. Guidelines from the American Academy of Pediatrics regarding the diagnosis and management of bronchiolitis (2014) also do not recommend inhaled corticosteroids or bronchodilators be routinely used in the management of bronchiolitis.[16]

302. **Chronic Cough due to Bronchiectasis.** Limited data are available with budesonide/formoterol (foreign formulation of Symbicort) for the treatment of non-cystic fibrosis (CF) bronchiectasis.[17,18] ACCP guidelines note that in patients with bronchiectasis due to CF or other causes, treatment of respiratory infections and airway clearance techniques are the mainstays of management.[27] In patients with airflow obstruction and/or bronchial hyperreactivity (e.g., asthma and/or COPD), bronchodilators may be of benefit.[11,19] However, the ACCP guidelines and the British Thoracic Society (BTS) guidelines do not recommend treatment with ICSs. Bronchiectasis guidelines from the European Respiratory Society also recommend against offering ICSs to adult

patients with bronchiectasis.[20] There may be a role for combination ICS/LABA therapy in patients with coexisting asthma or COPD, but there is no evidence to support this therapy in patients without these concomitant conditions.[19,20]

303. Whooping Cough/Pertussis. There are no data to support the use of ICS/LABA combination therapy in treating this condition. According to the ACCP guidelines, LABAs and corticosteroids should not be offered to patients with whooping cough as there is no evidence to suggest benefit.[11] Although short-acting beta-agonists (SABA) [along with other treatments] have been proposed as standard treatment for whooping cough, one review article reported that treatment with the SABA salbutamol resulted in no change in coughing.[21]

304. Angiotensin-Converting Enzyme (ACE) Inhibitor-Induced Cough. There are no data to support the use of ICS/LABA combination therapy in treating this condition. Discontinuation of the ACE inhibitor is the only uniformly effective treatment for ACE inhibitor-induced cough. In those patients in whom the ACE inhibitor cannot be discontinued, pharmacologic therapy aimed at suppressing cough should be attempted. ICSs and beta-agonists are not recommended therapeutic options.[11]

305. Psychogenic Cough/Habit Cough/Tic Cough. There are no data to support the use of ICS/LABA combination therapy in treating these conditions. Non-pharmacological therapies, such as behavior modification, hypnosis and psychiatric therapy are the mainstays of treatment.[11,22]

306. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No changes.	05/23/2018
Annual Revision	Policy updated to include generics to Advair Diskus.	06/12/2019
Update	8/26/2019: • Automation: removed "inhaled combinations of these agents" as surrogate markers for the diagnosis of asthma or COPD.	NA
Annual Revision	• Policy Statement: o Noted that Wixela Inhub, a generic to Advair Diskus with its own brand name, is included in the policy. • Automation: o Added specific ICD-10 codes used in Automation to Appendix A. • Conditions Recommended for Approval: o Moved Chronic Bronchitis and Emphysema from "Other Uses with Supportive Evidence" to "FDA-Approved Indications". • Conditions Not Recommended for Approval: o Changed "Treatment of Symptoms Associated with a Current Rhinovirus Infection/Cough Associated with a Current Episode of the Common Cold" to "Acute Cough Associated with the Common Cold". o Changed "Treatment of Chronic Cough due to Gastroesophageal Reflux Disease (GERD): to "Chronic Cough due to Gastroesophageal Reflux Disease (GERD)". o Changed "Treatment of Symptoms due to an Acute Respiratory Infection" to "Acute Cough due to an Acute Respiratory Infection". o Changed "Treatment of Chronic Cough due to Bronchiolitis" to "Chronic Cough due to Bronchiolitis". o Changed "Treatment of Chronic Cough due to Bronchiectasis" to "Chronic Cough due to Bronchiectasis".	07/01/2020
Selected Revision	Policy updated to include AirDuo Digihaler.	09/16/2020
Update	Date: 12/01/2020 No criteria changes. Policy updated to include budesonide/formoterol fumarate inhalation aerosol (authorized generic to Symbicort).	NA

APPENDIX A

ICD-10 Codes Automated for Asthma and COPD

ICD-10 Codes	Code Description
J41*	Simple and mucopurulent chronic bronchitis
J41.0	Simple chronic bronchitis
J41.1	Mucopurulent chronic bronchitis
J41.8	Mixed simple and mucopurulent chronic bronchitis
J42	Unspecified chronic bronchitis
J43*	Emphysema
J43.0	Unilateral pulmonary emphysema (MacLeod's syndrome)
J43.1	Panlobular emphysema
J43.2	Centrilobular emphysema
J43.8	Other emphysema
J43.9	Emphysema, unspecified
J44*	Other chronic obstructive pulmonary disease
J44.0	Chronic obstructive pulmonary disease with (acute) lower respiratory infection
J44.1	Chronic obstructive pulmonary disease with (acute) exacerbation
J44.9	Chronic obstructive pulmonary disease, unspecified
J45*	Asthma
J45.2*	Mild intermittent asthma
J45.20	Mild intermittent asthma, uncomplicated
J45.21	Mild intermittent asthma with (acute) exacerbation
J45.22	Mild intermittent asthma with status asthmaticus
J45.3*	Mild persistent asthma
J45.30	Mild persistent asthma, uncomplicated
J45.31	Mild persistent asthma with (acute) exacerbation
J45.32	Mild persistent asthma with status asthmaticus
J45.4*	Moderate persistent asthma
J45.40	Moderate persistent asthma, uncomplicated
J45.41	Moderate persistent asthma with (acute) exacerbation
J45.42	Moderate persistent asthma with status asthmaticus
J45.5*	Severe persistent asthma
J45.50	Severe persistent asthma, uncomplicated
J45.51	Severe persistent asthma with (acute) exacerbation
J45.52	Severe persistent asthma with status asthmaticus
J45.9*	Other and unspecified asthma
J45.90*	Unspecified asthma
J45.901	Unspecified asthma with (acute) exacerbation
J45.902	Unspecified asthma with status asthmaticus
J45.909	Unspecified asthma, uncomplicated
J45.99*	Other asthma
J45.990	Exercise induced bronchospasm
J45.991	Cough variant asthma
J45.998	Other asthma

COPD – Chronic obstructive pulmonary disease; * Indicates the inclusion of subheadings.

PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary – Daliresp Prior Authorization Policy

- Daliresp® (roflumilast tablets – Astra Zeneca)

REVIEW DATE: 11/11/2020

OVERVIEW

Daliresp, a selective phosphodiesterase-4 (PDE-4) inhibitor, is indicated as a treatment to reduce the risk of **chronic obstructive pulmonary disease** (COPD) exacerbations in patients with severe COPD

associated with chronic bronchitis and a history of exacerbations.[1] Daliresp is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

Clinical Efficacy

Daliresp has been studied in patients currently receiving treatment with bronchodilators (e.g., long-acting $beta_2$-agonists [LABAs]) and inhaled corticosteroids (ICSs) with or without additional therapy with a long-acting muscarinic antagonist (LAMA).[2-7] Five placebo-controlled clinical trials evaluated the effect of Daliresp on COPD exacerbations.[1-7] Two of these studies initially included patients with severe COPD with chronic bronchitis and/or emphysema; in both studies, Daliresp did not demonstrate a significant reduction in COPD exacerbation rates. An exploratory analysis of these trials found that in the subgroup of patients with severe COPD who had chronic bronchitis and exacerbations within the previous year, Daliresp resulted in better exacerbation reduction than in the overall population. Two subsequent trials were conducted involving patients with severe COPD, chronic bronchitis, and at least one COPD exacerbation within the previous year. In both trials, Daliresp demonstrated a significant reduction in the rate of moderate or severe exacerbations compared to placebo.

Guidelines

The 2020 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for the diagnosis, management, and prevention of COPD recommend bronchodilators and inhaled corticosteroids as initial pharmacological treatment.[8] Following initiation, therapies should be adjusted as needed based on symptom severity and exacerbation risk. Daliresp is recommended in patients who continue to experience exacerbations despite LAMA/ LABA combination therapy and have a blood eosinophil level < 100 cells/microliter. Low blood eosinophils are predictive of an insufficient response to ICS therapy, thereby making Daliresp a good option. Daliresp is also listed as a possible therapeutic option in patients receiving triple therapy with an ICS/LAMA/LABA who have an forced expiratory volume in 1 second (FEV_1) < 50% and chronic bronchitis, and continue to experience exacerbations (especially if the patient has been hospitalized for one or more COPD exacerbations in the past year).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Daliresp. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Daliresp is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Chronic Obstructive Pulmonary Disease (COPD).** Approve Daliresp for 3 years if the patient meets the following criteria (A, B, C, and D):
   - **A)** Patient has severe COPD or very severe COPD, according to the prescriber; AND
   - **B)** Patient has a history of exacerbations; AND
   - **C)** Patient meets ONE of the following (i or ii):
     - **i.** Patient has chronic bronchitis AND has tried an inhaled long-acting $beta_2$-agonist, an inhaled long-acting muscarinic antagonist, and an inhaled corticosteroid concomitantly; OR
     - **ii.** Patient has tried an inhaled long-acting muscarinic antagonist and long-acting $beta_2$-agonist concomitantly AND has a blood eosinophil level < 100 cells/microliter.

Note: Use of a combination inhaler containing multiple agents from the medication classes listed would fulfil the requirement. Examples of an inhaled long-acting beta$_2$-agonists include Arcapta Neohaler, Serevent Diskus, Striverdi Respimat, Brovana, and Perforomist. Examples of a long-acting muscarinic antagonists include Incruse Ellipta, Seebri Neohaler, Spiriva HandiHaler, Spiriva Respimat, Tudorza Pressair, Lonhala Magnair, and Yupelri. Examples of inhaled corticosteroids include Alvesco, ArmonAir Digihaler, Arnuity Ellipta, Asmanex Twisthaler/HFA, Flovent Diskus/HFA, Pulmicort Flexhaler, Qvar RediHaler, and budesonide suspension for inhalation (Pulmicort Respules, generics). Examples of inhaled corticosteroid/long-acting beta$_2$-agonist combination inhalers include Advair Diskus (generic Wixela Inhub; authorized generics), Breo Ellipta, and Symbicort. Examples of long-acting muscarinic antagonist/long-acting beta$_2$-agonist combination inhalers include Anoro Ellipta, Bevespi Aerosphere, Duaklir Pressair, Stiolto Respimat, and Utibron Neohaler. Examples of corticosteroid/long-acting beta$_2$-agonist/long-acting muscarinic antagonist combination inhalers are Breztri Aerosphere and Trelegy Ellipta.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Daliresp is not recommended for the following situations:

307. **Asthma.** The efficacy of roflumilast (formulation not specified) in patients with asthma[9-11], allergic asthma[12,13], and exercise-induced asthma[14] has been evaluated. More data are needed to define the place in therapy of Daliresp in the treatment of asthma. Current asthma guidelines from the Global Initiative for Asthma Prevention (GINA) [2020] and the European Respiratory Society (ERS)/American Thoracic Society (ATS) [2014] Global Strategy for Asthma Management and Prevention do not address Daliresp as a recommended therapy for asthma management.[15,16]

308. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Chronic Obstructive Pulmonary Disease (COPD):** Criteria updated to clarify that patient must try LABA, LAMA, and ICS together as combination therapy prior to approval of Daliresp.	10/24/2018
Annual Revision	**Chronic Obstructive Pulmonary Disease (COPD):** Added criteria to allow for approval for patients who have chronic bronchitis AND has tried an inhaled long-acting beta$_2$-agonist, an inhaled long-acting muscarinic antagonist, and an inhaled corticosteroid concomitantly (previously in place) OR patients who have tried an inhaled long-acting muscarinic antagonist and long-acting beta$_2$-agonist concomitantly AND has a blood eosinophil level < 100 cells/microliter. Wording in reference to "according to the prescribing physician" was changed to "according to the prescriber".	10/23/2019
Annual Revision	**Chronic Obstructive Pulmonary Disease (COPD):** No changes to criteria. Updated list of examples of inhaled long-acting beta$_2$-agonists, long-acting muscarinic antagonists, and corticosteroids.	11/11/2020

COPD – Chronic obstructive pulmonary disease; LABA – Long-acting beta agonist; LAMA – Long-acting muscarinic antagonist; ICS – Inhaled corticosteroid.

PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Adempas Prior Authorization Policy
- Adempas® (riociguat tablets – Bayer)

REVIEW DATE: 09/23/2020

OVERVIEW

Adempas, a soluble guanylate cyclase (sGC) stimulator, is indicated for the treatment of adults with:[1]
- **Chronic thromboembolic pulmonary hypertension** (CTEPH) [World Health Organization {WHO} Group 4], persistent/recurrent, after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class.
- **Pulmonary Arterial Hypertension** (PAH) [WHO Group 1), to improve exercise capacity, WHO functional class, and to delay clinical worsening.

Disease Overview

PAH is a serious but rare condition impacting approximately fewer than 20,000 patients in the US. It is classified within Group 1 pulmonary hypertension among the five different groups that are recognized. In this progressive disorder the small arteries in the lungs become narrowed, restricted, or blocked causing the heart to work harder to pump blood, leading to activity impairment.[2,3] In time, right-sided heart failure and/or death may occur. Common PAH symptoms include shortness of breath, fatigue, chest pain, dizziness and fainting, along with impairment in activity tolerance. It is more prevalent in women. Patients of all

ages may develop the disease; however, the mean age of diagnosis typically happens between 36 to 50 years. Children may also have PAH. The condition may occur due to various underlying medical conditions or as a disease that uniquely impacts the pulmonary circulation; both genetic and environmental factors may be involved. PAH is defined as a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg with a pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg measured by cardiac catheterization. The prognosis in PAH has been described as poor, with the median survival being approximately 3 years. However, primarily due to advances in pharmacological therapies, the long-term prognosis has improved. Lung transplantation may be recommended if pharmacological or medical therapies fail, based upon patient status. The WHO categorizes PAH into stages, which is also referred to as the functional class (Class I to IV) and is an adaptation of the New York Heart Association (NYHA) system to evaluate activity tolerance.

CTEPH is a persistent obstruction of pulmonary arteries and is often a complication of pulmonary embolism.[4,5] It is classified within Group 4 pulmonary hypertension. Symptoms include progressive dyspnea on exertion, as well as fatigue, syncope, hemoptysis, and signs of right heart failure. Pulmonary endarterectomy is the treatment of choice for most patients with CTEPH. However, around 40% of patients are deemed inoperable for various reasons. Medication therapy, including Adempas, may also be recommended. Anticoagulant therapy is also given.

Guidelines

In 2019, an updated CHEST guideline and Expert Panel Report regarding therapy for pulmonary arterial hypertension in adults was released.[5] Evidence for use of the many medications available is also detailed. Adempas is cited as a vital therapy in the management of PAH with several benefits in a variety of clinical scenarios.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Adempas. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Adempas as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: In the *Pulmonary Arterial Hypertension – Adempas Prior Authorization Policy*, documentation is required for initiation of therapy where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and catheterization laboratory reports. For a patient case in which the documentation requirement of the right heart catheterization upon prior authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement in this *Pulmonary Arterial Hypertension – Adempas Prior Authorization Policy* is considered to be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Adempas is recommended in those who meet the following criteria:

FDA-Approved Indication

34. **Chronic Thromboembolic Pulmonary Hypertension (CTEPH).** Approve for 3 years if prescribed by, or in consultation with, a pulmonologist or a cardiologist.

35. Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1]. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 years if the patient meets all of the following criteria (i, ii, and iii):
- **i.** Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
- **ii.** Patient meets the following criteria (a and b):
  - **a)** Patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND
  - **b)** Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND
- **iii.** Medication is prescribed by, or in consultation with, a cardiologist or a pulmonologist.

B) Patient is Currently Receiving Adempas. Approve for 3 years if the patient meets all of the following criteria (i, ii, and iii):
- **i.** Patient has a diagnosis of WHO Group 1 PAH; AND
- **ii.** Patient meets the following criteria (a and b):
  - **a)** Patient has had a right heart catheterization; AND
  - **b)** Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND
- **iii.** Medication is prescribed by, or in consultation with, a cardiologist or a pulmonologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Adempas is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	For initial review, documentation is required for the right heart catheterization. For patients who are currently receiving Adempas, the wording "or who are receiving another medication for WHO Group 1 PAH" was removed, along with the cited alternatives. Also, the requirement was added that the patient has had a right heart catheterization and that the results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH. A note was added in the documentation section that for a patient case in which the documentation requirement of the right heart catheterization upon prior authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement is considered to be met.	08/22/2018
Annual Revision	No criteria changes.	09/11/2019
Annual Revision	No criteria changes.	09/23/2020

PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Endothelin Receptor Antagonists
- Letairis® (ambrisentan tablets – Gilead, generics)
- Opsumit® (macitentan tablets – Actelion)
- Tracleer® (bosentan tablets [generic] and tablets for oral suspension – Actelion)

REVIEW DATE: 09/23/2020

OVERVIEW

Letairis, Opsumit and Tracleer are oral endothelin receptor antagonists indicated for the treatment of pulmonary arterial hypertension (PAH) World Health Organization (WHO) Group 1.[1-3] Letairis is indicated to improve exercise ability and delay clinical worsening as well as for use in combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability.[2] Opsumit is noted to reduce the risks of disease progression and hospitalization for PAH.[3] Tracleer is indicated in adults to improve exercise ability and decrease the rate of clinical worsening and in pediatric patients ≥ 3 years of age with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability.[1]

The BENEFiT (Bosentan Effects in iNopErable Forms of chronic Thromboembolic pulmonary hypertension) study was a double-blind trial involving patients with chronic thromboembolic pulmonary hypertension (CTEPH) who were randomized to Tracleer or placebo for 16 weeks (n = 156). Benefits were noted in some hemodynamic parameters (e.g., decreased PVR).[4] Adempas® (riociguat tablets), a soluble guanylate cyclase stimulator, is the only agent indicated for the treatment of adults with CTEPH (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class.[5] The agent is also indicated for the treatment of adults with PAH (WHO Group 1). Adempas has a Boxed Warning regarding embryofetal toxicity and is contraindicated in patients using nitrates or nitric oxide donors in any forms, as well as in patients using phosphodiestase inhibitors. The main adverse event associated with Adempas is symptomatic hypotension.

Tracleer has been used in patients with systemic sclerosis who have digital ulcers.[6-13] In a prospective, multicenter, placebo-controlled, double-blind study patients (n = 122) with limited or diffuse systemic sclerosis (scleroderma) were randomized in a 2:1 ratio to receive Tracleer or placebo for 16 weeks.[6] Patients receiving Tracleer had a 48% reduction in the mean number of new ulcerations (1.4 vs. 2.7 new ulcers; P = 0.0083), the primary efficacy endpoint. The effect was more substantial in patients with digital ulcers at study entry. However, no differences were noted in the healing of established ulcers.[6] Another trial showed a reduction in the occurrence of new digital ulcers in patients given Tracleer for 24 weeks.[10] Many other agents are utilized in digital ulcers.[8,14,15]

Disease Overview

PAH is a serious but rare condition impacting approximately fewer than 20,000 patients in the US. It is classified within Group 1 pulmonary hypertension among the five different groups that are recognized. In this progressive disorder the small arteries in the lungs become narrowed, restricted, or blocked causing the heart to work harder to pump blood, leading to activity impairment.[16,17] In time, right-sided heart failure and/or death may occur. Common PAH symptoms include shortness of breath, fatigue, chest pain, dizziness and fainting, along with impairment in activity tolerance. It is more prevalent in women. Patients of all ages may develop the disease; however, the mean age of diagnosis typically happens between 36 to 50 years. Children may also have PAH. The condition may occur due to various underlying medical

conditions or as a disease that uniquely impacts the pulmonary circulation; both genetic and environmental factors may be involved. PAH is defined as a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg with a pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg measured by cardiac catheterization. The prognosis in PAH has been described as poor, with the median survival being approximately 3 years. However, primarily due to advances in pharmacological therapies, the long-term prognosis has improved. Lung transplantation may be recommended if pharmacological or medical therapies fail, based upon patient status. The WHO categorizes PAH into stages, which is also referred to as the functional class (Class I to IV) and is an adaptation of the New York Heart Association (NYHA) system to evaluate activity tolerance.

CTEPH is a persistent obstruction of pulmonary arteries and is often a complication of pulmonary embolism.[18,19] It is classified within Group 4 pulmonary hypertension. Symptoms include progressive dyspnea on exertion, as well as fatigue, syncope, hemoptysis, and signs of right heart failure. Pulmonary endarterectomy is the treatment of choice for most patients with CTEPH. However, around 40% of patients are deemed inoperable for various reasons. Medication therapy may also be recommended. Anticoagulant therapy is also given.

Guidelines

Various guidelines address endothelin receptor antagonists.

- **Pulmonary Arterial Hypertension:** In 2019, an updated CHEST guideline and Expert Panel Report regarding therapy for pulmonary arterial hypertension in adults details many medications. It was noted that endothelin receptor antagonists play a vital role and have various benefits in the management of PAH.[17]
- **Systemic Sclerosis:** In 2017 the European League Against Rheumatism (EULAR) updated recommendations for the treatment of systemic sclerosis.[12] Tracleer should be considered to reduce the number of new digital ulcers in systemic sclerosis, especially in patients who have multiple digital ulcers despite use of calcium channel blockers, phosphodiesterase type 5 inhibitors or iloprost therapy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Letairis, Opsumit, and Tracleer. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with these agents, as well as the monitoring required for adverse events and long-term efficacy, approval requires the agents to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: In the *Pulmonary Arterial Hypertension – Endothelin Receptor Antagonists Prior Authorization Policy*, documentation is required for initiation of therapy where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and catheterization laboratory reports. For a patient case in which the documentation requirement of the right heart catheterization upon Prior Authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement in this *Pulmonary Arterial Hypertension – Endothelin Receptor Antagonist Prior Authorization Policy* is considered to be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Letairis, Opsumit, and Tracleer is recommended in those who meet the following criteria:

FDA-Approved Indication

36. Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1]. Approve for the duration noted if the patient meets ONE of the following (A or B):

C) Initial Therapy. Approve for 3 years if the patient meets all of the following criteria (i, ii, and iii).

i. Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

ii. Patient meets the following criteria (a and b):

a) Patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND

b) Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

iii. The medication is prescribed by or in consultation with a cardiologist or a pulmonologist.

D) Patient is Currently Receiving the Requested Endothelin Receptor Antagonist (i.e., Letairis, Opsumit, or Tracleer). Approve for 3 years if the patient meets the following criteria (i, ii, and iii):

iv. Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

v. Patient meets the following criteria (a and b):

a) Patient has had a right heart catheterization; AND

b) Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

vi. The medication is prescribed by, or in consultation with, a cardiologist or a pulmonologist.

Other Uses with Supportive Evidence

Coverage of Tracleer is also recommended in those who meet the following criteria:

37. Chronic Thromboembolic Pulmonary Hypertension (CTEPH). Approve Tracleer for 3 years if the patient meets the following criteria (A and B):

A) Patient meets one of the following criteria (i, ii, or iii):

i. Patient has tried Adempas; OR

ii. Patient has a specific contraindication to use of Adempas according to the prescriber; OR
Note: Examples of contraindications to use of Adempas include that the patient is receiving nitrates or nitric oxide donors, the patient is receiving a phosphodiesterase inhibitor such as sildenafil or tadalafil, or that the patient is hypotensive or is at risk for hypotension.

iii. Patient is currently receiving Tracleer.

B) The medication is prescribed by, or in consultation with, a cardiologist or a pulmonologist.

38. Digital Ulcers/Systemic Sclerosis. Approve Tracleer for 3 years if the patient meets the following criteria (A or B):

A) Patient has tried two other therapies for this condition such as calcium channel blockers (CCBs), phosphodiesterase type 5 (PDE5) inhibitors, alpha-adrenergic blockers, nitroglycerin, or angiotensin converting enzyme (ACE) inhibitors; OR
Note: Examples of CCBs include amlodipine, felodipine, and nifedipine; an example of an alpha-adrenergic blocker is prazosin; and examples of PDE5 inhibitors include sildenafil and Levitra® (vardenafil tablets).

B) Patient has tried one vasodilator/prostanoid therapy.
Note: Examples of vasodilator/prostanoid therapies include epoprostenol injection and alprostadil injection.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Letairis, Opsumit, and Tracleer is not recommended in the following situations:

309. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Tracleer® tablets and oral suspension [prescribing information]. South San Francisco, CA: Actelion Pharmaceuticals, May 2019.
2. Letairis® tablets [prescribing information]. Foster City, CA: Gilead Sciences; August 2019.
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15. Cruz JE, Ward A, Anthony S, et al. Evidence for the use of epoprostenol to treat Raynaud's phenomenon with or without digital ulcers: a review of the literature. *Ann Pharmacother*. 2016;50(12):1060-1067.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Selected Revision	Selected revision to add Tracleer oral suspension to the policy. No criteria changes were made.	02/07/2018
Annual Revision	For initial review, documentation is required for the right heart catheterization. For patients who are currently receiving the requested endothelin receptor antagonist, the wording "or who are receiving another medication for WHO Group 1 PAH" was removed, along with the cited alternatives. Also, the requirement was added that the patient has had a right heart catheterization and that the results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH. A note was added in the documentation section that for a patient case in which the documentation requirement of the right heart catheterization upon prior authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement is considered to be met.	08/22/2018
Update	04/10/2019: No criteria changes. Selected revision to add that generics are available to Letairis (tablets).	---
Annual Revision	No criteria changes. Medication alternatives are now listed as notes.	09/11/2019

Annual Revision	**Chronic Thromboembolic Pulmonary Hypertension:** For Tracleer the criteria regarding "patient has a specific contraindication to use of Adempas" wording was changed from "according to the prescribing physician" to "according to the prescriber."	09/23/2020

WHO – World Health Organization; PAH – Pulmonary arterial hypertension.

PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Epoprostenol Products Prior Authorization Policy

- Flolan® (epoprostenol injection – GlaxoSmithKline, generic)
- Veletri® (epoprostenol injection – Actelion)

REVIEW DATE: 09/23/2020

OVERVIEW

Epoprostenol injection, a prostacyclin vasodilator, is indicated for the treatment of pulmonary arterial hypertension (PAH) [World Health Organization {WHO} Group 1] to improve exercise capacity.[1-3]

Epoprostenol injection has been used with varying results in patients with chronic thromboembolic pulmonary hypertension (CTEPH).[4-6] It is sometimes used as a bridge prior to surgery. Limited options are available for patients with CTEPH.

Disease Overview

PAH is a serious but rare condition impacting fewer than 20,000 patients in the US. It is classified within Group 1 pulmonary hypertension among the five different groups that are recognized. In this progressive disorder the small arteries in the lungs become narrowed, restricted, or blocked causing the heart to work harder to pump blood, leading to activity impairment.[7,8] In time, right-sided heart failure and/or death may occur. Common PAH symptoms include shortness of breath, fatigue, chest pain, dizziness and fainting, along with impairment in activity tolerance. It is more prevalent in women. Patients of all ages may develop the disease; however, the mean age of diagnosis typically happens between 36 to 50 years. Children may also have PAH. The condition may occur due to various underlying medical conditions or as a disease that uniquely impacts the pulmonary circulation; both genetic and environmental factors may be involved. PAH is defined as a mean pulmonary artery pressure $\geq$ 25 mmHg with a pulmonary capillary wedge pressure $\leq$ 15 mmHg measured by cardiac catheterization. The prognosis in PAH has been described as poor, with the median survival being approximately 3 years. However, primarily due to advances in pharmacological therapies, the long-term prognosis has improved. Lung transplantation may be recommended if pharmacological or medical therapies fail, based upon patient status. The WHO categorizes PAH into stages, which is also referred to as the functional class (Class I to IV) and is an adaptation of the New York Heart Association system to evaluate activity tolerance.

CTEPH is a persistent obstruction of pulmonary arteries and is often a complication of pulmonary embolism.[9,10] It is classified within Group 4 pulmonary hypertension. Symptoms include progressive dyspnea on exertion, as well as fatigue, syncope, hemoptysis, and signs of right heart failure. Pulmonary endarterectomy is the treatment of choice for most patients with CTEPH. However, around 40% of patients are deemed inoperable for various reasons. Medication therapy may also be recommended. Anticoagulant therapy is also given.

Guidelines

In 2019, and updated CHEST guideline and Expert Panel Report regarding therapy for pulmonary arterial hypertension in adults was released.[8] Evidence for use of the many medications available is also detailed. In the absence of contraindications, patients with PAH should undergo acute vasoreactivity testing utilizing a short-acting agent (e.g., calcium channel blockers). For patients in Functional Class II, oral therapies are recommended such as endothelin receptor antagonists (Letairis® [ambrisentan tablets], Tracleer® [bosentan tablets], Opsumit® [macitentan tablets]), phosphodiesterase type 5 (PDE 5) inhibitors (tadalafil, sildenafil), and Adempas® (riociguat tablets). It is suggest that parenteral or inhaled prostanoids not be chosen as initial therapy for treatment naïve-patients with PAH with WHO Functional Class II symptoms or as second-line agents for patients with PAH with WHO Functional Class II who have not met their treatment goals. Parenteral prostanoids are recommended for patients with PAH in Functional Class III and IV.

Safety

Epoprostenol should not be abruptly discontinued or have the dose rapidly decreased as rebound pulmonary hypertension may occur.[1-3]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of epoprostenol injection. All approvals are provided for 1 year in duration unless otherwise noted below. Specifically, approvals will remain at 14 days for patients currently receiving the agent with inadequate information or if the criteria are not met. Because of the specialized skills required for evaluation and diagnosis of patients treated with epoprostenol injection as well as the monitoring required for adverse events and long-term efficacy, approval requires epoprostenol injection to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: In the *Pulmonary Arterial Hypertension – Epoprostenol Prior Authorization Policy*, documentation is required for initiation of therapy where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and catheterization laboratory reports. For a patient case in which the documentation requirement of the right heart catheterization upon prior authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement in this *Pulmonary Arterial Hypertension – Epoprostenol Prior Authorization Policy* is considered to be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of epoprostenol injection is recommended in those who meet the following criteria:

FDA-Approved Indication

39. Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1]. Approve for the duration noted if the patient meets ONE of the following (A or B):

- **A)** Initial Therapy. Approve for 1 year if the patient meets all of the following criteria (i, ii, iii, iv, and v):
  - **i.** Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
  - **ii.** Patient meets the following criteria (a and b):
    - **a)** Patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND

b) Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

iii. Patient meets ONE of the following criteria (a or b):

a) Patient is in Functional Class III or IV; OR

b) Patient is in Functional Class II and meets ONE of the following criteria [(1) or (2)]:

(1) Patient has tried or is currently receiving one oral agent for PAH; OR
Note: Examples of oral agents for PAH include Tracleer® (bosentan tablets), Letairis® (ambrisentan tablets [generic]), Opsumit® (macitentan tablets), Adempas® (riociguat tablets), Revatio® (sildenafil tablets and suspension [generics]), Adcirca® (tadalafil tablets [generic]), Orenitram® (treprostinil extended-release tablets), Alyq™ (tadalafil tablets), and Uptravi® (selexipag tablets).

(2) Patient has tried one inhaled or parenteral prostacyclin product for PAH; AND
Note: Examples of inhaled and parenteral prostacyclin products for PAH include Remodulin® (treprostinil injection [generic]), Ventavis® (iloprost inhalation solution), and Tyvaso® (treprostinil inhalation solution).

iv. Patient with idiopathic PAH must meet ONE of the following criteria (a, b, c, d, or e):

a) Patient must meet both of the following [(1) and (2)]:

(1) According to the prescriber, the patient has had an acute response to vasodilator testing that occurred during the right heart catheterization; AND
Note: An example of a response can be defined as a decrease in mean pulmonary artery pressure of at least 10 mm Hg to an absolute mean pulmonary artery pressure of less than 40 mm Hg without a decrease in cardiac output.

(2) Patient has tried one oral calcium channel blocker (CCB) therapy; OR
Note: Examples of CCBs include amlodipine and nifedipine extended-release tablets.

b) According to the prescriber, the patient did not have an acute response to vasodilator testing; OR

c) According to the prescriber, the patient cannot undergo a vasodilator test; OR

d) Patient cannot take CCB therapy; OR
Note: Examples of reasons a patient cannot take CCB therapy include right heart failure or decreased cardiac output.

e) Patient has tried one CCB; AND
Note: Examples of CCBs include amlodipine and nifedipine extended-release tablets.

v. Medication is prescribed by or in consultation with a cardiologist or a pulmonologist; OR

B) Patient Currently Receiving Epoprostenol. Approve for the duration noted below if the patient meets the following criteria (i or ii):

i. Approve for 1 year if the patient meets ALL of the following conditions (a, b, and c):

a) Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

b) Patient meets the following criteria [(1) and (2)]:

(1) Patient has had a right heart catheterization; AND

(2) Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

c) Medication is prescribed by, or in consultation with, a cardiologist or a pulmonologist; OR

ii. Approve a short-term supply of epoprostenol for up to 14 days if the patient does not meet the criteria in 1Bi above or if there is insufficient information available. These cases must be forwarded immediately to the pharmacist for review.
Note: A 14-day supply should be sufficient to address coverage issues. However, multiple short-term approvals are allowed if a coverage determination cannot be made. Abrupt discontinuation of epoprostenol therapy may have severe adverse consequences.

Other Uses with Supportive Evidence

40. **Chronic Thromboembolic Pulmonary Hypertension (CTEPH).** Approve for 1 year if prescribed by, or in consultation with, a pulmonologist or a cardiologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of epoprostenol injection (Flolan, Veletri, generics) is not recommended in the following situations:

1. **Chronic Obstructive Pulmonary Disease (COPD) in a Patient Without PAH (WHO Group 1).** COPD is classified as Group 3 Pulmonary Hypertension (pulmonary hypertension associated with lung diseases and/or hypoxia). Pulmonary hypertension may develop late in the course of COPD, but medications used for the treatment of PAH (WHO Group 1) are not recommended therapies.[11]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	For initial review, documentation is required for the right heart catheterization and the result confirms the diagnosis of WHO Group 1 PAH. The specific values required from the heart catheterization test were removed. For patients currently receiving epoprostenol a right heart catheterization is required and the results should confirm the diagnosis of WHO Group 1 PAH, but documentation is not required, nor are the specific values required. For patients in Functional Class II, the exceptions to use of other medications was removed as these can be handled on a case by case basis. Viagra and Cialis were removed from the listing of medications for WHO Group 1 PAH. A note was added in the documentation section that for a patient case in which the documentation requirement of the right heart catheterization upon prior authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement is considered to be met. Criteria	08/22/2018

	that provided a 14 day approval for patients currently receiving epoprostenol for any indication were removed.	
Annual Revision	For the indications for PAH (WHO Group 1) and chronic thromboembolic pulmonary hypertension, the approval durations were changed from 3 years to 1 year. However, the short-term up to 14 day approval duration for PAH still remains for patients who are receiving therapy but do not meet criteria or in those with insufficient information. Listing of examples of medications are in criteria are now listed in notes.	09/11/2019
Annual revision	The word "Products" was added to the Policy name. For criteria regarding patients with idiopathic PAH, the wording "According to the prescriber" was added for the criterion regarding that the patient has had an acute response to vasodilator testing that occurred during the right heart catheterization. Also, examples of a definition of response were moved from the criteria to a Note. Also, the wording "According to the prescriber" were added to the criterion stating that the patient did not have an acute response to vasodilator testing, as well as to the criterion that the patient cannot undergo a vasodilator test. For the criterion stating that the "Patient cannot take a calcium channel blocker therapy", examples were moved from the criteria to a Note. Alyq (tadalafil tablets) was added as an example of oral agent used for PAH in the note for the criteria regarding PAH.	09/23/2020

PAH – Pulmonary arterial hypertension WHO – World Health Organization.

PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Inhaled Prostacyclin Products

- Ventavis® (iloprost inhalation solution – Actelion)
- Tyvaso® (treprostinil inhalation solution – United Therapeutics)

REVIEW DATE: 09/23/2020

OVERVIEW

Ventavis and Tyvaso are both inhaled prostacyclin vasodilators indicated for the treatment of pulmonary arterial hypertension (PAH).[1,2] Ventavis is indicated for the treatment of PAH (World Health Organization [WHO] Group 1) to improve a composite endpoint consisting of exercise tolerance, symptoms (based on New York Heart Association [NYHA] Class), and lack of deterioration. Tyvaso is indicated for the treatment of PAH (WHO Group 1) to improve exercise ability.[2]

Disease Overview

PAH is a serious but rare condition impacting approximately fewer than 20,000 patients in the US. It is classified within Group 1 pulmonary hypertension among the five different groups that are recognized. In this progressive disorder the small arteries in the lungs become narrowed, restricted, or blocked causing the heart to work harder to pump blood, leading to activity impairment.[3,4] In time, right-sided heart failure and/or death may occur. Common PAH symptoms include shortness of breath, fatigue, chest pain, dizziness and fainting, along with impairment in activity tolerance. It is more prevalent in women. Patients of all ages may develop the disease; however, the mean age of diagnosis typically happens between 36 to 50 years. Children may also have PAH. The condition may occur due to various underlying medical conditions or as a disease that uniquely impacts the pulmonary circulation; both genetic and environmental factors may be involved. PAH is defined as a mean pulmonary artery pressure (mPAP) $\geq$ 25 mmHg with a pulmonary capillary wedge pressure (PCWP) $\leq$ 15 mmHg measured by cardiac catheterization. The prognosis in PAH has been described as poor, with the median survival being approximately 3 years. However, primarily due to advances in pharmacological therapies, the long-term prognosis has improved. Lung transplantation may be recommended if pharmacological or medical therapies fail, based upon patient status. The WHO categorizes PAH into stages, which is also referred to as the functional class (Class I to IV) and is an adaptation of the New York Heart Association (NYHA) system to evaluate activity tolerance.

Guidelines

An updated treatment algorithm (2013) by the 2nd World Symposium on Pulmonary Hypertension (WSPH) states that patients with Functional Class II should be treated initially with oral therapies (e.g., Adempas® [riociguat tablets], Revatio® (sildenafil tablets and suspension [generics] {Note: brand name Revatio injection also available}), Adcirca® [tadalafil tablets {generic}], Opsumit® [macitentan tablets], Tracleer® [bosentan tablets], and Letairis® [ambrisentan tablets]).[5] Ventavis and Tyvaso are recommended for patients in Functional Class III and IV. In situations of inadequate response, combination therapy (including double or triple therapy) is recommended.

In 2019, and updated CHEST guideline and Expert Panel Report regarding therapy for pulmonary arterial hypertension in adults was released.[4] Evidence for use of the many medications available is also detailed. One recommendation is that parenteral or inhaled prostanoids should not be used as initial therapy for patients with PAH who are treatment naïve with WHO Functional Class II symptoms or as second-line agents for patients with PAH with WHO Functional Class II symptoms who have not met original treatment goals.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ventavis and Tyvaso. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ventavis and Tyvaso as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: In the *Pulmonary Arterial Hypertension – Inhaled Prostacyclin Products Prior Authorization Policy*, documentation is required for initiation of therapy where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and catheterization laboratory reports. For a patient case in which the documentation requirement of the right heart catheterization upon prior authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement in this *Pulmonary Arterial Hypertension – Inhaled Prostacyclin Products Prior Authorization Policy* is considered to be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ventavis and Tyvaso is recommended in those who meet the following criteria:

FDA-Approved Indications

41. Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1]. Approve for the duration noted if the patient meets ONE of the following (A or B):

- **A)** Initial Therapy. Approve for 3 years if the patient meets the following criteria (i, ii, iii, and iv):
  - **i.** Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
  - **ii.** Patient meets one of the following (a or b):
    - **a)** Patient is in Functional Class III or IV; OR
    - **b)** Patient is in Functional Class II and meets ONE of the following criteria [(1) or (2)]:
      - **(1)** Patient has tried or is currently receiving one oral agent for PAH; OR
        Note: Examples of oral agents for PAH include Tracleer® (bosentan tablets), Letairis® (ambrisentan tablets [generic]), Opsumit® (macitentan tablets), Revatio® (sildenafil

tablets and suspension [generics]), Adcirca® (tadalafil tablets [generic]), Alyq™ (tadalafil tablets), Adempas® (riociguat tablets), Orenitram® (treprostinil extended-release tablets), and Uptravi® (selexipag tablets).

(2) Patient has tried one inhaled or parenteral prostacyclin product for PAH; AND
Note: Examples of inhaled and parenteral prostacyclin products for PAH include Tyvaso® (treprostinil inhalation solution), Ventavis® (iloprost inhalation solution), Remodulin® (treprostinil injection [generic]), and epoprostenol injection (Flolan®, Veletri®, generics); AND

iii. Patient meets the following criteria (a and b):
- **a)** The patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND
- **b)** The results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

iv. Medication is prescribed by, or in consultation with, a cardiologist or a pulmonologist.

B) Patient is Currently Receiving the Requested Inhaled Prostacyclin for PAH (i.e., Ventavis or Tyvaso). Approve for 3 years if the patient meets the following criteria (i, ii, and iii):

i. Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

ii. Patient meets the following criteria (a and b):
- **a)** Patient has had a right heart catheterization; AND
- **b)** Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

iii. Medication is prescribed by, or in consultation with, a cardiologist or a pulmonologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ventavis and Tyvaso are not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

534. Ventavis® inhalation solution [prescribing information]. South San Francisco, CA: Actelion Pharmaceuticals; December 2019.
535. Tyvaso® inhalation solution [prescribing information]. Research Triangle Park, NC: United Therapeutics Corp.; October 2017.
536. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension: A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association Developed in Collaboration with the American College of Chest Physicians: American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol*. 2009;53:1573-1619.
537. Klinger JR, Elliott CG, Levine DJ, et al. Therapy for pulmonary arterial hypertension in adults. Update of the CHEST guideline and Expert Panel Report. *CHEST*. 2019;155(3):565-586.
538. Galie N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl):D60-D72.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	For initial review, documentation is required for the right heart catheterization. Also, in the criteria for initial therapy, for patients in functional class II for the criteria that requires a trial of an oral agent, the exceptions to use of therapy were removed (the patient is unable to take any of the oral agents [e.g., those with liver abnormalities {Tracleer}, patient of childbearing potential {Tracleer, Letairis}, concomitant use with nitrates {sildenafil, Adcirca/Cialis}, hypotension, drug-drug interactions) as these can	08/22/2018

	be handled on an exception basis. For this criteria, Viagra and Cialis were removed as oral options (Revatio and Adcirca are now available as generics). For patients who are currently receiving the requested inhaled prostacyclin product, the wording "or who are receiving another medication for WHO Group 1 PAH" was removed, along with the cited alternatives. Also, the requirement was added that the patient has had a right heart catheterization and that the results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH. A note was added in the documentation section that for a patient case in which the documentation requirement of the right heart catheterization upon prior authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement is considered to be met.	
Annual Revision	No criteria changes. Medication alternatives are now listed as notes.	09/11/2019
Annual Revision	No criteria changes. Alyq (tadalafil tablets) listed as an example of an oral medication for PAH in a Note.	09/23/2020

PAH – Pulmonary arterial hypertension; WHO – World Health Organization.

PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Orenitram Prior Authorization Policy

- Orenitram® (treprostinil extended-release tablets – United Therapeutics)

REVIEW DATE: 09/23/2020

OVERVIEW

Orenitram, prostacyclin mimetic, is indicated for the treatment of pulmonary arterial hypertension (PAH) World Health Organization (WHO) Group 1 to delay disease progression and to improve exercise capacity.[1]

Disease Overview

PAH is a serious but rare condition impacting approximately fewer than 20,000 patients in the US. It is classified within Group 1 pulmonary hypertension among the five different groups that are recognized. In this progressive disorder the small arteries in the lungs become narrowed, restricted, or blocked causing the heart to work harder to pump blood, leading to activity impairment.[2,3] In time, right-sided heart failure and/or death may occur. Common PAH symptoms include shortness of breath, fatigue, chest pain, dizziness and fainting, along with impairment in activity tolerance. It is more prevalent in women. Patients of all ages may develop the disease; however, the mean age of diagnosis typically happens between 36 to 50 years. Children may also have PAH. The condition may occur due to various underlying medical conditions or as a disease that uniquely impacts the pulmonary circulation; both genetic and environmental factors may be involved. PAH is defined as a mean pulmonary artery pressure (mPAP) $\geq$ 25 mmHg with a pulmonary capillary wedge pressure (PCWP) $\leq$ 15 mmHg measured by cardiac catheterization. The prognosis in PAH has been described as poor, with the median survival being approximately 3 years. However, primarily due to advances in pharmacological therapies, the long-term prognosis has improved. Lung transplantation may be recommended if pharmacological or medical therapies fail, based upon patient status. The WHO categorizes PAH into stages, which is also referred to as the functional class (Class I to IV) and is an adaptation of the New York Heart Association (NYHA) system to evaluate activity tolerance.

Guidelines

In 2019, an updated CHEST guideline and Expert Panel Report regarding therapy for pulmonary arterial hypertension in adults was released.[3] Many other agents other than Orenitram are recommended as initial and subsequent therapy such as endothelin receptor antagonists (Letairis® [ambrisentan tablets], Tracleer® [bosentan tablets], Opsumit® [macitentan tablets], phosphodiesterase type 5 [PDE 5] inhibitors [tadalafil, sildenafil), and Adempas® (riociguat tablets). The addition of an oral prostanoid product is recommended

in patients with PAH who are in Functional Class III without evidence of rapid disease progression or a poor prognosis among those not willing or able to manage parenteral prostanoids.

Safety

Abrupt discontinuation or sudden large reductions in the dosage of Orenitram may cause PAH symptoms to worsen.[1] In the event of a planned short-term treatment interruption for patients unable to take oral medication, consider a temporary infusion of subcutaneous or intravenous treprostinil.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Orenitram. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Orenitram as well as the monitoring required for adverse events and long-term efficacy, approval requires Orenitram to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: In the *Pulmonary Arterial Hypertension – Orenitram Prior Authorization Policy*, documentation is required for initiation of therapy where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and catheterization laboratory reports. For a patient case in which the documentation requirement of the right heart catheterization upon prior authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement in this *Pulmonary Arterial Hypertension – Orenitram Prior Authorization Policy* is considered to be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Orenitram is recommended in those who meet the following criteria:

FDA-Approved Indication

42. Pulmonary Arterial Hypertension (World Health Organization [WHO] Group 1). Approve for the duration noted if the patient meets ONE of the following (A or B):

E) Initial Therapy. Approve for 3 years if the patient meets all of the following criteria (i, ii, iii, and iv):

- **i.** Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
- **ii.** Patient meets the following criteria (a and b):
  - **a)** Patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND
  - **b)** Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND
- **iii.** Patient meets one of the following conditions (a or b):
  - **a)** Patient has tried two oral therapies for PAH (or is currently receiving them) from two of the three following different categories (either alone or in combination) each for ≥ 60 days: one phosphodiesterase type 5 (PDE5) inhibitor, one endothelin receptor antagonist (ERA), or Adempas (riociguat tablets); OR
    Note: Examples of PDE5 inhibitors include Revatio® (sildenafil tablets and suspension [generic]), Adcirca® (tadalafil tablets [generic]) and Alyq™ (tadalafil tablets) and examples of ERAs include Tracleer® (bosentan tablets), Letairis® (ambrisentan tablets [generic]), and Opsumit® (macitentan tablets).
  - **b)** Patient is receiving or has received in the past one PAH prostacyclin therapy or a prostacyclin receptor agonist (i.e., Uptravi® [selexipag tablets]) for PAH; AND
    Note: Examples of prostacyclin therapies for PAH include Tyvaso® (treprostinil inhalation solution), Ventavis® (iloprost inhalation solution), Remodulin® (treprostinil injection [generic]), and epoprostenol injection [Flolan, Veletri, generics]); AND
- **iv.** Medication is prescribed by or in consultation with a cardiologist or a pulmonologist.

F) Patient is Currently Receiving Orenitram. Approve for 3 years if the patient meets all of the following criteria (i, ii, and iii):

vii. Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

viii. Patient meets the following criteria (a and b):

a) Patient has had a right heart catheterization; AND

b) Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH); AND

ix. The medication is prescribed by, or in consultation with, a cardiologist or a pulmonologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Orenitram is not recommended in the following situations:

310. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

539. Orenitram® extended-release tablets [prescribing information]. Research Triangle Park, NC: United Therapeutics Corporation; October 2019.
540. McLaughlin VV, Archer SL, Badesch DB, et al; Writing committee members. ACCF/AHA 2009 Expert consensus document on pulmonary hypertension: A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: Developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. *Circulation*. 2009;119:2250-2294.
541. Klinger JR, Elliott CG, Levine DJ, et al. Therapy for pulmonary arterial hypertension in adults. Update of the CHEST guideline and Expert Panel Report. *CHEST*. 2019;155(3):565-586.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	02/14/2018
Annual Revision	For initial review, documentation is required for the right heart catheterization. The criteria were deleted regarding patients "who are receiving another medication for WHO Group 1 PAH". For patients who are currently receiving Uptravi, the requirement was added that the patient has had a right heart catheterization and that the results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH. A note was added in the documentation section that for a patient case in which the documentation requirement of the right heart catheterization upon prior authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement is considered to be met.	08/22/2018
Annual Revision	No criteria changes. Medications alternatives are now listed in notes.	09/11/2019
Annual Revision	No criteria changes. Alyq (tadalafil tablets) added as an example of a phosphodiesterase type 5 inhibitor.	09/23/2020

WHO – World Health Organization; PAH – Pulmonary arterial hypertension.

PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Phosphodiesterase Type 5 Inhibitors Prior Authorization Policy

- Adcirca® (tadalafil tablets [generic] – Eli Lilly/United Therapeutics)
- Alyq™ (tadalafil tablets [generic] – Teva)
- Revatio® (sildenafil tablets [generic], suspension [generic], and injection – Pfizer)

REVIEW DATE: 09/23/2020

OVERVIEW

Adcirca and Revatio and are phosphodiesterase type 5 (PDE5) inhibitors indicated for the treatment of pulmonary arterial hypertension (PAH).[1,2] Alyq is a generic to Adcirca.[3] Adcirca and Alyq are indicated for the treatment of PAH (WHO Group I) to improve exercise ability.[2,3] Revatio is indicated for the treatment of PAH (World Health Organization [WHO] Group I) in adults to improve exercise ability and delay clinical worsening.

Disease Overview

PAH is a serious but rare condition impacting approximately fewer than 20,000 patients in the US. It is classified within Group 1 pulmonary hypertension among the five different groups that are recognized. In this progressive disorder the small arteries in the lungs become narrowed, restricted, or blocked causing the heart to work harder to pump blood, leading to activity impairment.[4,5] In time, right-sided heart failure and/or death may occur. Common PAH symptoms include shortness of breath, fatigue, chest pain, dizziness and fainting, along with impairment in activity tolerance. It is more prevalent in women. Patients of all ages may develop the disease; however, the mean age of diagnosis typically happens between 36 to 50 years. Children may also have PAH. The condition may occur due to various underlying medical conditions or as a disease that uniquely impacts the pulmonary circulation; both genetic and environmental factors may be involved. PAH is defined as a mean pulmonary artery pressure (mPAP) $\geq$ 25 mmHg with a pulmonary capillary wedge pressure (PCWP) $\leq$ 15 mmHg measured by cardiac catheterization. The prognosis in PAH has been described as poor, with the median survival being approximately 3 years. However, primarily due to advances in pharmacological therapies, the long-term prognosis has improved. Lung transplantation may be recommended if pharmacological or medical therapies fail, based upon patient status. The WHO categorizes PAH into stages, which is also referred to as the functional class (Class I to IV) and is an adaptation of the New York Heart Association (NYHA) system to evaluate activity tolerance.

Guidelines

In 2019, an updated CHEST guideline and Expert Panel Report regarding therapy for pulmonary arterial hypertension in adults was released.[5] Evidence for use of the many medications available is also detailed. PDE5 inhibitors are a vital therapy in the management of PAH with several benefits in a variety of clinical scenarios.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Adcirca, Alyq, and Revatio. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Adcirca, Alyq, and Revatio, as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: In the *Pulmonary Arterial Hypertension – Phosphodiesterase Type 5 Inhibitors Prior Authorization Policy*, documentation is required for initiation of therapy where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and catheterization laboratory reports. For a patient case in which the documentation requirement of the right heart catheterization upon Prior Authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement in this *Pulmonary Arterial Hypertension – Phosphodiesterase Type 5 Inhibitors Prior Authorization Policy* is considered to be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Revatio tablets, Revatio suspension, sildenafil suspension, Revatio injection, Adcirca, and Alyq is recommended in those who meet the following criteria:

FDA-Approved Indication

I. Coverage of Adcirca tablets, Alyq tablets, Revatio suspension, Revatio tablets, and sildenafil suspension is recommended in those who meet the following criteria:

43. Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1]. Approve for the duration noted if the patient meets ONE of the following (A or B):

G) Initial Therapy. Approve for 3 years if the patient meets all of the following criteria (i, ii, and iii):

- **i.** Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
- **ii.** Patient meets the following criteria (a and b):
  - **a)** Patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND
  - **b)** Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND
- **iii.** The medication is prescribed by, or in consultation with, a cardiologist or a pulmonologist.

H) Patient Currently Receiving the Requested Phosphodiesterase Type 5 (PDE5) inhibitor (i.e., Adcirca, Alyq, Revatio suspension, Revatio tablets, or sildenafil suspension). Approve for 3 years if the patient meets the following criteria (i, ii, and iii):

- **x.** Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
- **xi.** Patient meets the following criteria (a and b):
  - **a)** Patient has had a right heart catheterization; AND
  - **b)** Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND
- **xii.** The medication is prescribed by, or in consultation with, a cardiologist or a pulmonologist.

II. Coverage of Revatio injection is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1].** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve Revatio injection for 3 years if the patient meets the following criteria (i, ii, iii, and iv):
     - **i.** Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
     - **ii.** Patient is unable to take an oral PDE5 inhibitor indicated for WHO Group 1 PAH; AND
       Note: Examples of oral PDE5 inhibitors for PAH include Revatio® (sildenafil tablets or suspension or suspension [generics]), Adcirca® (tadalafil tablets [generic]), and Alyq™ (tadalafil tablets]).
     - **iii.** Patient meets the following criteria (a and b):
       - **a)** Patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND
       - **b)** Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND
     - **iv.** The medication is prescribed by, or in consultation with, a cardiologist or a pulmonologist.
   - **B)** Patient Currently Receiving Revatio Injection. Approve Revatio injection for 3 years if the patient meets the following criteria (i, ii, iii, and iv):
     - **i.** Patient has a diagnosis of World Health Organization (WHO) Group 1 PAH; AND
     - **ii.** Patient is unable to take an oral PDE5 inhibitor indicated for WHO Group 1 PAH; AND
       Note: Examples of oral PDE5 inhibitors for PAH include Adcirca® (tadalafil tablets [generic]), Alyq™ (tadalafil tablets), and Revatio® (sildenafil tablets or suspension [generics]); AND
     - **iii.** Patient meets the following criteria (a and b):
       - **a)** Patient has had a right heart catheterization; AND
       - **b)** Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND
     - **iv.** The medication is prescribed by, or in consultation with, a cardiologist or a pulmonologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Adcirca, Alyq, Revatio injection, Revatio suspension, Revatio tablets, and sildenafil suspension is not recommended in the following situations:

2. **Erectile Dysfunction.** Coverage is not recommended. Patients should use other PDE5 inhibitors indicated for erectile dysfunction (i.e., Viagra® [sildenafil tablets], Cialis® [tadalafil tablets]).[6,7]

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

6. Revatio® tablets, oral suspension, and injection [prescribing information]. New York, NY: Pfizer; February 2020.
7. Adcirca® tablets [prescribing information]. Indianapolis, IN: Eli Lilly (marketed by United Therapeutics Corporation); August 2017.
8. Alyq™ tablets [prescribing information]. North Wales, PA: Teva Pharmaceuticals; January 2019.
9. McLaughlin VV, Archer SL, Badesch DB, et al; Writing committee members. ACCF/AHA 2009 Expert consensus document on pulmonary hypertension: A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: Developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. *Circulation*. 2009;119:2250-2294.
10. Klinger JR, Elliott CG, Levine DJ, et al. Therapy for pulmonary arterial hypertension in adults. Update of the CHEST guideline and Expert Panel Report. *CHEST*. 2019;155(3):565-586.

11. Viagra® tablets [prescribing information]. New York, NY: Pfizer Labs; December 2017.
12. Cialis® tablets [prescribing information]. Indianapolis, IN: Eli Lilly; February 2018.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	For initial review, documentation is required for the right heart catheterization. For patients who are currently receiving the currently requested phosphodiesterase type 5 inhibitor or Revatio injection, the wording "or who are receiving another medication for WHO Group 1 PAH" was removed, along with the cited alternatives. Also, the requirement was added that the patient has had a right heart catheterization and that the results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH. A note was added in the documentation section that for a patient case in which the documentation requirement of the right heart catheterization upon prior authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement is considered to be met. For Revatio injection, the previous criteria that required that the patient be unable to taken an oral PDE5 inhibitor was changed to the patient cannot take an oral PDE5 inhibitor indicated for WHO Group 1 PAH (Viagra was removed as an alternative).	08/22/2018
Update	06/17/2019: No criteria changes. Generic sildenafil suspension was added to the policy.	--
Annual Revision	No criteria changes. The listing of examples is now as a note in the criteria.	09/18/2019
Annual Revision for the PSM	No changes.	09/25/2019
Update	05/28/2019: No criteria changes. Alyq added to the Policy (generic to Adcirca).	--
Annual Revision	No criteria changes. Alyq was added as an example of an oral phosphodiesterase type 5 inhibitor.	09/23/2020
Annual Revision for the PSM	No criteria changes. Alyq (tadalafil tablets) added to examples of phosphodiesterase type 5 inhibitors in related criteria.	09/23/2020

WHO – World Health Organization; PAH – Pulmonary arterial hypertension; PSM – Preferred Specialty Management.

PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Remodulin Prior Authorization Policy

- Remodulin® (treprostinil injection for subcutaneous or intravenous use – United Therapeutics Corporation, generic)

REVIEW DATE: 09/23/2020

OVERVIEW

Treprostinil injection, a prostacyclin vasodilator, is indicated for the treatment of pulmonary arterial hypertension (PAH) [World Health Organization {WHO} Group 1] to:[1,2]

- **Diminish symptoms associated** with exercise.
- **Reduce the rate of clinical deterioration** for patients who require transition from epoprostenol.

Treprostinil injection has been used with varying results in patients with chronic thromboembolic pulmonary hypertension (CTEPH).[3-7] Benefits noted include improvement in functional class, six-minute walk distance, and in hemodynamic parameters. Treprostinil injection is sometimes used as a bridge prior to surgery. Limited options are available for patients with CTEPH.

Disease Overview

PAH is a serious but rare condition impacting fewer than 20,000 patients in the US. It is classified within Group 1 pulmonary hypertension among the five different groups that are recognized. In this progressive

disorder the small arteries in the lungs become narrowed, restricted, or blocked causing the heart to work harder to pump blood, leading to activity impairment.[8,9] In time, right-sided heart failure and/or death may occur. Common PAH symptoms include shortness of breath, fatigue, chest pain, dizziness and fainting, along with impairment in activity tolerance. It is more prevalent in women. Patients of all ages may develop the disease; however, the mean age of diagnosis typically happens between 36 to 50 years. Children may also have PAH. The condition may occur due to various underlying medical conditions or as a disease that uniquely impacts the pulmonary circulation; both genetic and environmental factors may be involved. PAH is defined as a mean pulmonary artery pressure $\geq$ 25 mmHg with a pulmonary capillary wedge pressure $\leq$ 15 mmHg measured by cardiac catheterization. The prognosis in PAH has been described as poor, with the median survival being approximately 3 years. However, primarily due to advances in pharmacological therapies, the long-term prognosis has improved. Lung transplantation may be recommended if pharmacological or medical therapies fail, based upon patient status. The WHO categorizes PAH into stages, which is also referred to as the functional class (Class I to IV) and is an adaptation of the New York Heart Association system to evaluate activity tolerance.

CTEPH is a persistent obstruction of pulmonary arteries and is often a complication of pulmonary embolism.[10,11] It is classified within Group 4 pulmonary hypertension. Symptoms include progressive dyspnea on exertion, as well as fatigue, syncope, hemoptysis, and signs of right heart failure. Pulmonary endarterectomy is the treatment of choice for most patients with CTEPH. However, around 40% of patients are deemed inoperable for various reasons. Medication therapy may also be recommended. Anticoagulant therapy is also given.

Guidelines

In 2019, and updated CHEST guideline and Expert Panel Report regarding therapy for PAH in adults was released.[9] Evidence for use of the many medications available is also detailed. In the absence of contraindications, patients with PAH should undergo acute vasoreactivity testing utilizing a short-acting agent (e.g., calcium channel blockers). For patients in Functional Class II, oral therapies are recommended such as endothelin receptor antagonists (Letairis® [ambrisentan tablets], Tracleer® [bosentan tablets], Opsumit® [macitentan tablets]), phosphodiesterase type 5 (PDE 5) inhibitors (tadalafil, sildenafil), and Adempas® (riociguat tablets). It is suggested that parenteral or inhaled prostanoids not be chosen as initial therapy for treatment naïve patients with PAH with WHO Functional Class II symptoms or as second-line agents for patients with PAH with WHO Functional Class II who have not met their treatment goals. Parenteral prostanoids are recommended for patients with PAH in Functional Class III and IV.

Safety

Treprostinil injection should not be abruptly discontinued or have the dose rapidly decreased as rebound pulmonary hypertension may occur.[1,2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of treprostinil injection. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with treprostinil injection as well as the monitoring required for adverse events and long-term efficacy, approval requires treprostinil injection to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: In the *Pulmonary Arterial Hypertension – Remodulin Authorization Policy*, documentation is required for initiation of therapy where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and catheterization laboratory reports. For a patient case in which the documentation requirement of the right heart catheterization upon Prior Authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement in this *Pulmonary Arterial Hypertension – Remodulin Prior Authorization Policy* is considered to be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of treprostinil injection is recommended in those who meet the following criteria:

FDA-Approved Indication

44. Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1]. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 year if the patient meets all of the following criteria (i, ii, iii, iv, and v):

- **i.** Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
- **ii.** Patient meets the following criteria (a and b):
  - **a)** Patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND

b) Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

iii. Patient meets ONE of the following criteria (a or b):

a) Patient is in Functional Class III or IV; OR

b) Patient is in Functional Class II and meets ONE of the following criteria [(1) or (2)]:

(1) Patient has tried or is currently receiving one oral agent for PAH; OR
Note: Examples of oral agents for PAH include Tracleer® (bosentan tablets), Letairis® (ambrisentan tablets [generic]), Opsumit® (macitentan tablets), Adempas® (riociguat tablets), Revatio® (sildenafil tablets and oral suspension [generics]), Adcirca® (tadalafil tablets [generic]), Alyq™ (tadalafil tablets), Orenitram® (treprostinil extended-release tablets) and Uptravi® (selexipag tablets).

(2) Patient has tried one inhaled or parenteral prostacyclin product for PAH; AND
Note: Examples of inhaled and parenteral prostacyclin products for PAH include Ventavis® (iloprost inhalation solution), Tyvaso® (treprostinil inhalation solution), and epoprostenol injection (Flolan, Veletri, generic).

iv. Patient with idiopathic PAH must meet ONE of the following criteria (a, b, c, d, or e):

a) Patient meets both of the following criteria [(1) and (2)]:

(1) According to the prescriber, the patient has had an acute response to vasodilator testing that occurred during the right heart catheterization; AND
Note: An example of a response can be defined as a decrease in mean pulmonary artery pressure of at least 10 mm Hg to an absolute mean pulmonary artery pressure of less than 40 mm Hg without a decrease in cardiac output.

(2) Patient has tried one calcium channel blocker (CCB) therapy; OR
Note: Examples of CCBs include amlodipine and nifedipine extended-release tablets.

b) According to the prescriber, the patient did not have an acute response to vasodilator testing; OR

c) According to the prescriber, the patient cannot undergo a vasodilator test; OR

d) Patient cannot take CCB therapy; OR
Note: Examples of reasons a patient cannot take CCB therapy include right heart failure or decreased cardiac output.

e) Patient has tried one CCB; AND
Note: Examples of CCBs include amlodipine and nifedipine extended-release tablets.

v. Medication is prescribed by, or in consultation with, a cardiologist or a pulmonologist; OR

B) Patient Currently Receiving Remodulin. Approve for the duration noted below if the patient meets the following criteria (i or ii):

iii. Approve for 1 year if the patient meets ALL of the following conditions (a, b, and c):

d) Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

e) Patient meets the following criteria [(1) and (2)]:

(1) Patient has had a right heart catheterization; AND

(2) Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

f) Medication is prescribed by, or in consultation with, a cardiologist or a pulmonologist; OR

iv. Approve a short-term supply of Remodulin for up to 14 days if the patient does not meet the criteria in 1Bi above or if there is insufficient information available. These cases must be forwarded immediately to the pharmacist for review.
Note: A 14-day supply should be sufficient to address coverage issues. However, multiple short-term approvals are allowed if a coverage determination cannot be made. Abrupt discontinuation of Remodulin therapy may have severe adverse consequences.

Other Uses with Supportive Evidence

45. Chronic Thromboembolic Pulmonary Hypertension (CTEPH). Approve for 1 year if prescribed by or in consultation with a pulmonologist or a cardiologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of treprostinil injection is not recommended in the following situations:

3. Chronic Obstructive Pulmonary Disease (COPD) in a Patient without PAH (WHO Group 1). COPD is classified as Group 3 Pulmonary Hypertension (pulmonary hypertension associated with lung diseases and/or hypoxia). Pulmonary hypertension may develop late in the course of COPD, but medications used for the treatment of PAH (WHO Group 1) are not recommended therapies.[12]

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

542. Remodulin® for subcutaneous or intravenous use [prescribing information]: Research Triangle Park, NC: United Therapeutics Corp; July 2018.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	For initial review, documentation is required for the right heart catheterization and the results confirm the diagnosis of WHO Group 1 PAH. The specific values required from the heart catheterization test were removed. For patients currently receiving Remodulin, a right heart catheterization is required and the results should confirm the diagnosis of WHO Group 1 PAH, but documentation is not required, nor are the specific values required. For patients in Functional Class II, the exceptions to use of other medications was removed as these can be handled on a case by case basis. Viagra and Cialis were removed from the listing of medications for WHO Group 1 PAH as Revatio and Adcirca are available generically. A note was added in the documentation section that for a patient case in which the documentation requirement of the right heart	08/22/2018

	catheterization upon prior authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement is considered to be met. Criteria that provided a 14-day approval for patients currently receiving Remodulin for any indication were removed.	
Update	04/10/2019: No criteria changes. Note that Remodulin is available as a generic.	--
Annual Revision	For the indications for PAH (WHO Group 1) and chronic thromboembolic pulmonary hypertension, the approval durations were changed from 3 years to 1 year. However, the short-term up to 14-day approval duration for PAH still remains for patients who are receiving therapy but do not meet criteria or in those with insufficient information. The medication examples are now listed as a note.	09/11/2019
Annual Revision	For criteria regarding patients with idiopathic PAH, the wording "According to the prescriber" was added for the criterion regarding that the patient has had an acute response to vasodilator testing that occurred during the right heart catheterization. Also, examples of a definition of response were moved from the criteria to a Note. Also, the wording "According to the prescriber" were added to the criterion stating that the patient did not have an acute response to vasodilator testing, as well as to the criterion that the patient cannot undergo a vasodilator test. For the criterion stating that the "Patient cannot take a calcium channel blocker therapy", examples were moved from the criteria to a Note. Alyq™ (tadalafil tablets) was added as an example of an oral agent used for PAH in the note for the criteria regarding PAH.	09/23/2020

PAH – Pulmonary arterial hypertension; WHO – World Health Organization.

PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Uptravi Prior Authorization Policy

- Uptravi® (selexipag tablets – Actelion)

REVIEW DATE: 09/23/2020

OVERVIEW

Uptravi, a prostacycline receptor agonist, is indicated for the treatment of pulmonary arterial hypertension (PAH) World Health Organization (WHO) Group 1 to delay disease progression and reduce the risk of hospitalization for PAH.[1]

Disease Overview

PAH is a serious but rare condition impacting approximately fewer than 20,000 patients in the US. It is classified within Group 1 pulmonary hypertension among the five different groups that are recognized. In this progressive disorder the small arteries in the lungs become narrowed, restricted, or blocked causing the heart to work harder to pump blood, leading to activity impairment.[2,3] In time, right-sided heart failure and/or death may occur. Common PAH symptoms include shortness of breath, fatigue, chest pain, dizziness and fainting, along with impairment in activity tolerance. It is more prevalent in women. Patients of all ages may develop the disease; however, the mean age of diagnosis typically happens between 36 to 50 years. Children may also have PAH. The condition may occur due to various underlying medical conditions or as a disease that uniquely impacts the pulmonary circulation; both genetic and environmental factors may be involved. PAH is defined as a mean pulmonary artery pressure (mPAP) $\geq$ 25 mmHg with a pulmonary capillary wedge pressure (PCWP) $\leq$ 15 mmHg measured by cardiac catheterization. The prognosis in PAH has been described as poor, with the median survival being approximately 3 years. However, primarily due to advances in pharmacological therapies, the long-term prognosis has improved. Lung transplantation may be recommended if pharmacological or medical therapies fail, based upon patient status. The WHO categorizes PAH into stages, which is also referred to as the functional class (Class I to IV) and is an adaptation of the New York Heart Association (NYHA) system to evaluate activity tolerance.

Guidelines/Recommendations

In 2019, an updated CHEST guideline and Expert Panel Report regarding therapy for pulmonary arterial hypertension in adults was released.[3] Many other agents other than Uptravi are recommended as initial and subsequent therapy such as endothelin receptor antagonists (Letairis® [ambrisentan tablets], Tracleer® [bosentan tablets], Opsumit® [macitentan tablets], phosphodiesterase type 5 [PDE 5] inhibitors [tadalafil, sildenafil), and Adempas® (riociguat tablets). The addition of an oral prostanoid product is recommended in patients with PAH who are in Functional Class III without evidence of rapid disease progression or a poor prognosis among those not willing or able to manage parenteral prostanoids.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Uptravi. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Uptravi as well as the monitoring required for adverse events and long-term efficacy, approval requires Uptravi to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: In the *Pulmonary Arterial Hypertension – Uptravi Prior Authorization Policy*, documentation is required for initiation of therapy where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and catheterization laboratory reports. For a patient case in which the documentation requirement of the right heart catheterization upon Prior Authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement in this *Pulmonary Arterial Hypertension – Uptravi Prior Authorization Policy* is considered to be met.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Uptravi is recommended in those who meet the following criteria:

FDA-Approved Indication

46. Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1]. Approve for the duration noted if the patient meets ONE of the following (A or B):

I) Initial Therapy. Approve for 3 years if the patient meets the following criteria (i, ii, iii, and iv):

i. Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

ii. Patient meets the following criteria (a and b):

a) Patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND

b) Results for the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

iii. Patient meets ONE the of following conditions (a or b):

a) Patient has tried or is currently receiving at least one oral medication for PAH from one of the three following different categories (either alone or in combination) each for ≥ 60 days: one phosphodiesterase type 5 (PDE5) inhibitor, one endothelin receptor antagonist (ERA), or Adempas® (riociguat tablets); OR

Note: Examples of PDE5 inhibitors include Revatio® (sildenafil tablets and suspension [generic]), Adcirca® (tadalafil tablets [generic]) and Alyq™ (tadalafil tablets) and examples of ERAs include Tracleer® (bosentan tablets), Letairis® (ambrisentan tablets [generic]), and Opsumit® (macitentan tablets).

b) Patient is currently receiving, or has a history of receiving, one prostacyclin therapy for PAH; AND

Note: Examples of prostacyclin therapies for PAH include Orenitram® (treprostinil tablets), Tyvaso® (treprostinil inhalation solution), Ventavis® (iloprost inhalation solution), Remodulin® (treprostinil injection [generics]), and epoprostenol injection [Flolan, Veletri, generics]); AND

iv. The medication is prescribed by, or in consultation with, a cardiologist or a pulmonologist.

J) Patients Currently Receiving Uptravi. Approve for 3 years if the patient meets all of the following criteria (i, ii, and iii):

i. Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

ii. Patient meets the following criteria (a and b):

a) Patient has had a right heart catheterization; AND

b) Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

iii. The medication is prescribed by, or in consultation with, a cardiologist or a pulmonologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Uptravi is recommended in those who meet the following criteria:

311. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes	02/14/2018
Annual Revision	For initial review, documentation is required for the right heart catheterization. The criteria were deleted regarding patients "who are receiving another medication for WHO Group 1 PAH". For patients who are currently receiving Uptravi, the requirement was added that the patient has had a right heart catheterization and that the results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH. A note was added in the documentation section that for patients who had previously provided documentation of the right heart catheterization upon coverage review for a different medication indicated for WHO Group 1 PAH, this documentation requirement is considered to be met.	08/22/2018
Annual Revision	No criteria changes. Medication alternatives are now cited as a note.	09/11/2019
Selected Revision	For patients receiving initial therapy for PAH, the criteria were changed from requiring two oral medications from three of the following categories for ≥ 60 days (i.e., one phosphodiesterase type 5 [PDE5] inhibitor, one endothelin receptor antagonist [ERA]), or Adempas® [riociguat tablets]) to at least one oral medication from the previous list for ≥ 60 days.	02/12/2020
Annual Revision	No criteria changes. Alyq (tadalafil tablets) was added to the list of examples of oral a phosphodiesterase type 5 inhibitor used in PAH.	09/23/2020

WHO – World Health Organization; PAH – Pulmonary Arterial Hypertension.

POLICY: Qbrexza Prior Authorization Policy

- Qbrexza™ (glycopyrronium cloth 2.4% for topical use – Dermira)

REVIEW DATE: 10/21/2020

OVERVIEW

Qbrexza, an anticholinergic, is indicated for the topical treatment of primary axillary (i.e., underarm) hyperhidrosis in adult and pediatric patients ≥ 9 years of age.[1] Qbrexza is applied topically once every 24 hours to clean dry skin on the underarm areas only; it is not for use on other body areas.

Guidelines

There are currently no guidelines for the treatment of hyperhidrosis published by a professional society. However, the International Hyperhidrosis Society, an independent, non-profit organization, provides an algorithm for the treatment of axillary hyperhidrosis (updated 2018).[2] Topical antiperspirant therapy or Qbrexza are both listed as initial treatment choices.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Qbrexza. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Qbrexza is recommended in those who meet the following criteria:

FDA-Approved Indications

~~83.~~80. **Hyperhidrosis, Primary Axillary.** Approve for 1 year if the patient is ≥ 9 years of age.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Qbrexza is not recommended in the following situations:

312. **Hyperhidrosis, other than Primary Axillary.** Qbrexza is not intended for application to areas other than the axillae.[1]

313. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	09/12/2018
Annual Revision	No criteria changes.	10/09/2019
Annual Revision	No criteria changes.	10/21/2020

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Rituximab Intravenous Products Prior Authorization Policy

- Rituxan® (rituximab intravenous infusion – Genentech)
- Riabni™ (rituximab-arrx intravenous infusion – Amgen)
- Ruxience™ (rituximab-pvvr intravenous infusion – Pfizer)
- Truxima® (rituximab-abbs intravenous infusion – Celltrion/Teva)

REVIEW DATE: 06/03/2020; selected revision 01/06/2021

OVERVIEW

Rituximab products are CD20-directed cytolytic antibodies. All approved rituximab intravenous products are indicated for treatment of the following conditions:

- **Chronic lymphocytic leukemia** (CLL), in combination with fludarabine and cyclophosphamide (FC) for the treatment of patients with previously untreated and previously treated CD20-positive disease.
- **Granulomatosis with polyangitis** (GPA) [Wegener's granulomatosis {WG}] and **microscopic polyangiitis** (MPA) in adults, in combination with glucocorticoids.
- **Non-Hodgkin lymphoma** (NHL), for the following uses:
  - previously untreated follicular, CD20-positive disease, in combination with first-line chemotherapy, and in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as a single-agent maintenance therapy.
  - for relapsed or refractory, low-grade or follicular, CD20-positive, B-cell, disease.
  - for non-progressing (including stable disease) low-grade, CD20-positive, B-cell disease as a single agent after first-line cyclophosphamide/vincristine/prednisone (CVP) chemotherapy.
  - for previously untreated diffuse large B-cell, CD20-positive disease, in combination with cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) or other anthracycline-based chemotherapy regimens.

In addition to the above indications, Rituxan intravenous and Truxima are also indicated for treatment of the following condition:

- **Rheumatoid arthritis**, in adult patients with moderately to severely active disease, in combination with methotrexate for patients who have had an inadequate response to one or more tumor necrosis factor inhibitors (TNFis).

In addition to the above indications, Rituxan intravenous is also indicated for treatment of the following conditions:

- **Granulomatosis with polyangitis** (GPA) [Wegener's granulomatosis {WG}] and **microscopic polyangiitis** (MPA) in patients ≥ 2 years of age, in combination with glucocorticoids.
- **Pemphigus vulgaris**, for adults with moderate to severe.

Rituximab products are monoclonal antibody directed specifically against the CD20 antigen found on the surface of normal and malignant B lymphocytes.[1-3] The antigen CD20 is expressed on > 90% of B-cell

NHLs. B-cells are thought to play a role in the pathogenesis of rheumatoid arthritis and associated chronic synovitis.

Ruxience and Truxima are approved as biosimilar to Rituxan intravenous, indicating no clinically meaningful differences in safety and effectiveness and the same mechanism of action, route of administration, dosage form, and strength as Rituxan IV. However, minor differences in clinically inactive components are allowed. At this time, Ruxience and Truxima has only demonstrated biosimilarity, not interchangeability.

Guidelines

The use of rituximab is supported in clinical guidelines in numerous situations, both as first-line therapy and in patients who are refractory or have relapsed following treatment with other therapies.[4-21]

- **Immune Thrombocytopenia (ITP):** Guidelines from the American Society of Hematology (ASH) for ITP (2011) mention rituximab as an appropriate agent for children and adolescents with ITP who have significant on-going bleeding despite treatment with intravenous immunoglobulin G (IVIG), anti-D, or corticosteroids.[17] Rituximab is also appropriate as an alternative to splenectomy in children/adolescents with chronic ITP or in patient who do not respond to splenectomy. In adults, rituximab in recommended for patients with ITP who are at risk for bleeding and who have failed one other line of therapy (e.g., corticosteroids, IVIG, splenectomy).
- **Multiple Sclerosis (MS):** In June 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[18] Rituximab is listed among various options, involving different mechanisms of action and modes of administration, which have shown benefits in patients with MS. The American Academy of Neurology has practice guidelines regarding disease-modifying therapies for adults with MS.[19] The guidelines mention rituximab for use in MS.
- **Neuromyelitis Optica Spectrum Disorders:** A review article lists rituximab as an effective treatment for neuromyelitis optica.[20]
- Oncology indications covered in National Comprehensive Cancer Network (NCCN) guidelines:[6]
    - **Acute Lymphoblastic Leukemia (ALL):** Guidelines (version 1.2020 – January 15, 2020) list rituximab in multiple induction regimens for Philadelphia chromosome (Ph)-negative disease.[11] In those with Ph-positive disease, rituximab should be considered in addition to chemotherapy for those with CD20-positive disease, especially in those < 60 years of age. Rituximab is also included in a regimen for relapsed/refractory disease for those with Ph-positive or –negative disease.
    - **B-Cell Lymphomas:** In the guidelines (version 1.2020 – January 22, 2020), rituximab is included in multiple treatment regimens across the spectrum of disease.[8] Guidelines for pediatric aggressive mature B-cell lymphomas (version 2.2020 – April 10, 2020) include rituximab intravenous among treatment regimens for induction therapy/initial treatment and as subsequent therapy for relapsed or refractory disease.[9] For primary cutaneous lymphomas (version 2.2020 – April 10, 2020), rituximab is a treatment option for patients with primary cutaneous B-cell lymphoma.[10]
    - **CLL/Small Lymphocytic Lymphoma:** Rituximab features prominently in the guidelines (version 4.2020 – December 20, 2019) and is included in multiple treatment regimens across the spectrum of disease.[7]
    - **Graft-Versus-Host Disease (GVHD):** Guidelines (version 2.2020 – March 23, 2020) list rituximab among the agents used for steroid-refractory chronic GVHD.[15]
    - **Hairy Cell Leukemia:** Guidelines (version 1.2020 – August 23, 2019) recommend rituximab in multiple regimens for relapsed/refractory disease, including in patients with progressive disease after relapsed/refractory therapy.[12]
    - **Hodgkin Disease:** Guidelines (version 2.2020 – April 17, 2020) recommend rituximab ± chemotherapy (depending on the clinical presentation) in the first-line setting for nodular

lymphocyte-predominant disease.[13] Rituximab is also used for relapsed/refractory disease and for maintenance.
    - **Waldenstrom Macroglobulinemia/lymphoplasmacytic lymphoma:** Guidelines (version 2.2020 – April 15, 2020) include rituximab in regimens across the spectrum of disease (primary therapy, previously treated disease, and maintenance).[14]
- **Rheumatoid Arthritis:** Guidelines from the American College of Rheumatology (ACR) [2015] have tumor inhibitors and non-TNF biologics (including rituximab), equally positioned following a trial of a conventional synthetic disease-modifying antirheumatic drug (DMARD).[16]
- **Systemic Lupus Erythematous (SLE):** European league Against Rheumatism (EULAR) recommendations for the management of systemic lupus erythematosus (2019) mention rituximab as a therapeutic option for patients who are refractory to standard immunosuppressive therapies.[21]
- **Vasculitis:** EULAR and European Renal Association/European Dialysis and Transplant Association (ERA-EDTA) recommendations for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis mention rituximab in combination with low-dose corticosteroids as a potential treatment option for remission-maintenance therapy.[4] Remission-maintenance therapy is recommended for at least 24 months following induction of sustained remission. British guidelines for use of rituximab in ANCA-associated vasculitis recommend rituximab for maintenance of remission to reduce the risk of relapse and its consequences.[5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of rituximab intravenous products. Because of the specialized skills required for evaluation and diagnosis of patients treated with rituximab as well as the monitoring required for adverse events and long-term efficacy, initial approval requires rituximab IV products to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration listed below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of rituximab intravenous products is recommended in those who meet the following criteria:

FDA-Approved Indications

29. Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

B) Induction Treatment. Approve for 1 month if the patient meets ALL of the following (i, ii, and iii):
   a. Patient has an ANCA-associated vasculotide; AND
      Note: Examples of ANCA-associated vasculitis include granulomatosis with polyangiitis (GPA) [Wegener's granulomatosis] or microscopic polyangiitis (MPA).
   ~~b.~~ The medication is being administered in combination with glucocorticoids; AND
   c. The medication is prescribed by or in consultation with a rheumatologist, nephrologist, or immunologist.

~~C)~~ Follow-Up Treatment of Patients Who Have Received Induction Treatment for ANCA-Associated Vasculitis. Approve for 1 year if the patient meets BOTH of the following (i and ii):
   Note: This includes a patient who received induction treatment using a rituximab product or other standard of care immunosuppressants.
   ~~a.~~ According to the prescriber, the patient achieved disease control with induction treatment; AND

~~b.~~ If the patient previously received a course of therapy, at least 16 weeks will elapse between courses.

30. B-Cell Lymphoma. Approve for 1 year if prescribed by or in consultation with an oncologist.
Note: Examples of B Cell Lymphomas include Follicular Lymphoma, Diffuse Large B-Cell Lymphoma, Acquired Immune Deficiency [AIDS]-Related B-Cell Lymphoma, Burkitt Lymphoma, Castleman's Disease, Marginal Zone Lymphoma (e.g., extranodal or MALT [gastric or nongastric], nodal, or splenic marginal zone lymphoma), Primary Mediastinal Large B-Cell Lymphoma, Mantle Cell Lymphoma, Post-Transplant Lymphoproliferative Disorders, Gray Zone Lymphoma, Primary Cutaneous B-Cell Lymphoma, Pediatric Aggressive Mature B-cell Lymphomas.

31. Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma. Approve for 1 year if prescribed by or in consultation with an oncologist.

32. Pemphigus Vulgaris. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Treatment. Approve for 1 month (which is adequate duration to administer one course of therapy) if the patient meets BOTH of the following (i and ii):
i. Therapy is initiated in combination with a corticosteroid unless contraindicated; AND
Note: An example of a corticosteroid is prednisone.
ii. The medication is prescribed by or in consultation with a dermatologist.
B) Patient is Being Treated of a Relapse or for Maintenance of Pemphigus Vulgaris. Approve for 1 year if the patient meets BOTH of the following (i and ii):
i. Subsequent infusions of will be administered no sooner than 16 weeks following the previous infusion of a rituximab product; AND
ii. The medication is prescribed by or in consultation with a dermatologist.

33. Rheumatoid Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 1 month (which is adequate duration to administer one course of therapy) if the patient meets ALL of the following conditions (i, ii, and iii):
i. Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND
Note: Examples of conventional synthetic disease-modifying antirheumatic drugs include methotrexate [oral or injectable], leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already has a 3-month trial at least one biologic. These patients who have already tried a biologic are not required to "step back" and try a conventional synthetic DMARD.
ii. The medication will not be used concurrently with another biologic or with a targeted synthetic DMARD; AND
Note: Examples of biologics include Cimzia, adalimumab products, etanercept products, infliximab products, Simponi Aria or subcutaneous, Actemra intravenous or subcutaneous, Kevzara, Kineret, and Orencia intravenous or subcutaneous. Examples of targeted synthetic DMARDs include Xeljanz/XR, Oluminat, and Rinvoq.
iii. The medication is prescribed by or in consultation with a rheumatologist.
B) Patient has already Received One or More Courses of a Rituximab Product for Rheumatoid Arthritis. Approve for 1 month (which is adequate duration to administer one course of therapy) if the patient meets BOTH of the following conditions (i and ii):
i. 16 weeks or greater will elapse between treatment courses; AND

Note: For example, there will be a minimum of 16 weeks since the first dose of the previous course and the first dose of the next course of a rituximab product.

ii. If the patient has already received two or more courses of therapy, the patient has responded to therapy as determined by the prescriber.
Note: Examples of a response include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids).

Other Uses with Supportive Evidence

6. Acute Lymphoblastic Leukemia. Approve for 1 year if the patient meets ALL of the following (A and B):
- **A)** Patient has CD20-positive disease; AND
- **B)** The medication is prescribed by or in consultation with an oncologist.

2. Graft-Versus-Host Disease. Approve for 1 year if the patient meets BOTH of the following (A and B):
- **i.** Patient has tried at least one conventional systemic treatment for graft versus host disease; AND
  Note: Examples include systemic corticosteroids (methylprednisolone, prednisone), cyclosporine, tacrolimus, mycophenolate mofetil, Imbruvica® (ibrutinib capsules and tablets), imatinib. antithymocyte globulin, Nipent® (pentostatin infusion), or an infliximab product.
- **ii.** The medication is prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center.

3. Hairy Cell Leukemia. Approve for 1 year if the patient meets BOTH of the following conditions (A and B):
- **A)** Patient has relapsed/refractory hairy cell leukemia; AND
- **B)** The medication is prescribed by or in consultation with an oncologist.

4. Hodgkin Lymphoma. Approve for 1 year if the patient meets BOTH of the following (A and B):
- **A)** Patient has nodular lymphocyte-predominant disease; AND
- **B)** The medication is prescribed by or in consultation with an oncologist.

10. Immune Thrombocytopenia (ITP). Approve if the patient meets ONE of the following (A or B):
- **A)** Initial Therapy. Approve for 1 month if the patient meets BOTH of the following (i and ii):
  - **i.** Patient has tried one other therapy; AND
    Note: Examples of therapies for ITP include intravenous immunoglobulin (IVIG), anti-D (RHO) immunoglobulin, corticosteroids, and splenectomy.
  - **ii.** The agent is prescribed by or in consultation with a hematologist.
- **B)** Patient has Already Received a Course of a Rituximab Product for ITP. Approve for 1 month if the patient meets ALL of the following (i, ii, and iii):
  - **i.** At least 6 months will elapse between treatment courses; AND
    Note: For example, there will be a minimum of 6 months separating the first dose of the previous course and the first dose of the requested course of a rituximab product.
  - **ii.** Patient responded to therapy as determined by the prescriber; AND
    Note: Examples of a response include a platelet count increase from baseline following treatment with a rituximab product.
  - **iii.** The prescriber has determined that the patient has relapsed.
    Note: Examples of a relapse include the patient experiences thrombocytopenia after achievement of a remission.

11. Multiple Sclerosis. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient has had an inadequate response or was unable to tolerate at least ONE other disease-modifying agent for multiple sclerosis; AND

B) The medication will not be used concurrently with another disease-modifying agent used for multiple sclerosis; AND

Note: Examples of disease-modifying agents for multiple sclerosis include Ocrevus (ocrelizumab IV infusion), Avonex (interferon beta-1a for intramuscular injection), Rebif (interferon beta-1a SC injection), Betaseron (interferon beta-1b SC injection), Extavia (interferon beta-1b SC injection), Copaxone (glatiramer acetate SC injection), Glatopa (glatiramer acetate SC injection), Plegridy (peginterferon beta-1a SC injection), Gilenya (fingolimod capsules), Aubagio (teriflunomide tablets), Tecfidera (dimethyl fumarate delayed-release capsules), or Lemtrada (alemtuzumab IV injection), mitoxantrone IV (Novantrone, generics), Tysabri (natalizumab IV injection), and Mavenclad (cladribine tablets).

C) The medication is prescribed by or in consultation with a physician who specializes in the treatment of MS and/or a neurologist; AND

D) At least 6 months will elapse between treatment courses.

Note: For example, if the patient has already received a course of therapy there will be a minimum of 6 months separating the first dose of the previous course and the first dose of the requested course of therapy.

1. Neuromyelitis Optica Spectrum Disorder. Approve for 1 month if prescribed by or in consultation with a neurologist.

13. Systemic Lupus Erythematous (SLE) [Lupus]. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 month (adequate duration to receive one course) if the patient meets BOTH of the following (i and ii):

i. Patient has tried at least ONE standard immunomodulating or immunosuppressant agent; AND
Note: Examples of standard immunomodulating or immunosuppressant agents include hydroxychloroquine, corticosteroids (e.g., prednisone, methylprednisolone), methotrexate, azathioprine, mycophenolate, and cyclophosphamide.

ii. The medication is prescribed by or in consultation with a rheumatologist, nephrologist, or neurologist.

B) Patient has Already Received a Course of a Rituximab Product for SLE. Approve for 1 month (adequate duration to receive one course) if 6 months or greater will elapse between treatment courses (i.e., there will be a minimum of 6 months separating the first dose of the previous rituximab course and the first dose of the requested course of rituximab).

14. Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma. Approve for 1 year if prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of rituximab intravenous products is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	New policy to replace the Inflammatory Conditions – Rituximab Intravenous Products for Rheumatoid Arthritis on 07/01/2020.	06/03/2020
Selected Revision	**Riabni:** This newly approved biosimilar was added to the policy. There are no changes to the criteria, which apply to all rituximab products included in this policy.	01/06/2021

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, PJIA, PsO, PsA, RA, SJIA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: PJIA, PSA, RA
		IV formulation: PJIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Ilaris (canakinumab SC injection**)**	Inhibition of IL-1β	SJIA
Kineret® (anakinra SC injection)	Inhibition of IL-1	RA, SJIA^
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; PJIA – Polyarticular juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; SJIA – Systemic juvenile idiopathic arthritis; UC – Ulcerative colitis; ^ Off-label use of SJIA supported in guidelines.

PRIOR AUTHORIZATION POLICY

POLICY: Scenesse Prior Authorization Policy

- Scenesse® (afamelanotide implant for subcutaneous use – Clinuvel)

REVIEW DATE: 02/10/2021

OVERVIEW

Scenesse, a melanocortin 1 receptor agonist, is indicated to increase pain-free light exposure in adults with a history of phototoxic reactions from **erythropoietic protoporphyria (EPP)**.[1] Scenesse is a controlled-release dosage form that is implanted subcutaneously (SC). Scenesse should be administered by a healthcare professional. A single implant which contains 16 mg of afamelanotide is inserted SC above the anterior supra-iliac crest once every 2 months.

Disease Overview

Porphyrias are disorders caused by enzyme defects in heme biosynthesis.[2] There are at least eight different types of porphyrias, which are classified as cutaneous or acute depending on the specific enzyme that is deficient. EPP is a cutaneous porphyria characterized by extreme photosensitivity. It is estimated to occur in 2 to 5 in 1,000,000 individuals.[3]

EPP occurs due to excessive accumulation of protoporphyrin, a heme precursor. Classic EPP is autosomal recessive and occurs due to a defect in the enzyme ferrochelatase, the final enzymatic step in heme biosynthesis.[4] An X-linked subtype of EPP, often referred as X-linked protoporphyria (XLP), accounts for 2% to 10% of all EPP cases. This type develops due to a gain-of-function mutation in an upstream enzyme in heme biosynthesis, leading to excess protoporphyrin production.[3,4] The two subtypes share the same biochemical and clinical features, although females with XLP may be less severely affected. Diagnosis is confirmed by one or both of the following: 1) biochemically via markedly elevated free erythrocyte protoporphyrin, and/or 2) molecular genetic testing.[2,3]

In both EPP subtypes, protoporphyrin accumulation in superficial skin vessels leads to phototoxicity upon light exposure, resulting in the hallmark symptoms of burning, tingling, and itching, which often occur without visible damage.[2-4] Phototoxic pain is not responsive to analgesics, including narcotics; management is focused on prevention of phototoxic episodes.[3]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Scenesse. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Scenesse as well as the monitoring required for adverse events and long-term efficacy, approval requires Scenesse to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Scenesse is recommended in those who meet the following criteria:

FDA-Approved Indications

260. Erythropoietic Protoporphyria (Including X-Linked Protoporphyria). Approve for 1 year if the patient meets the following criteria (A, B, C, and D):

- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has a history of at least one porphyric phototoxic reaction; AND
- **C)** The diagnosis is confirmed by at least one of the following (i or ii):
  - **i.** Free erythrocyte protoporphyrin level above the normal reference range for the reporting laboratory; OR
  - **ii.** Molecular genetic testing consistent with the diagnosis; AND
- **D)** The agent is prescribed by or in consultation with a dermatologist, gastroenterologist, hepatologist, or physician specializing in the treatment of cutaneous porphyrias.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Scenesse is not recommended in the following situations:

246. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	02/19/2020
Annual Revision	No changes to criteria.	02/10/2021

PRIOR AUTHORIZATION POLICY

POLICY: Sedative Hypnotics Medications for the InMynd Program

- doxepin 3 mg and 6 mg tablets (Silenor® – Somaxon Pharmaceuticals)
- eszopiclone tablets (Lunesta® – Sunovion Pharmaceuticals, generics)
- lemborexant (Dayvigo™ – Eisai)
- ramelteon (Rozerem® – Takeda)
- suvorexant (Belsomra® – Merck)
- zaleplon capsules (Sonata® – Pfizer, generics)
- zolpidem tablets (Ambien® – Sanofi-Aventis, generics)
- zolpidem extended-release tablets (Ambien CR® – Sanofi-Aventis, generics)
- zolpidem sublingual tablets (Edluar® – Meda Pharmaceuticals)

- zolpidem sublingual tablets (Intermezzo® – Purdue Pharma, generics)
- zolpidem oral spray (Zolpimist® –Aytu BioScience, Inc.)
- estazolam (Prosom® [brand obsolete], generics)
- flurazepam (Dalmane® [brand obsolete], generics)
- quazepam (Doral® – Galt Pharmaceuticals)
- temazepam (Restoril® – Mallinckrodt, generics)
- triazolam (Halcion® – Pfizer, generics)

DATE REVIEWED: 05/27/2020

OVERVIEW

Eszopiclone, zaleplon, zolpidem immediate-release (IR), zolpidem extended-release (ER), zolpidem sublingual tablets, Edluar, and Zolpimist are all non-benzodiazepine sedative hypnotics used for the treatment of insomnia.[1-7] These agents interact with gamma-aminobutyric acid (GABA) receptor complexes located closely to benzodiazepine receptors; the chemical structures of these agents are unrelated to the benzodiazepines. All are schedule IV controlled substances. Rozerem, another non-benzodiazepine sedative hypnotic, is a melatonin receptor agonist.[8] Silenor is a tricyclic compound that acts as a histamine H_1 receptor antagonist.[9] Neither Rozerem nor Silenor are controlled substances. Belsomra and Dayvigo are first-in-class orexin receptor antagonists and are schedule IV controlled substances.[10,11] Estazolam, flurazepam, Doral, temazepam, and triazolam are benzodiazepine sedative hypnotics indicated for the treatment of insomnia.[12] Benzodiazepines bind to receptors on the postsynaptic GABA neuron, and their effects appear to be linked to the GABA-A receptors.

Zolpidem IR, Edluar, Zolpimist, zaleplon, and the benzodiazepine sedative hypnotics are indicated for the short-term treatment of insomnia.[1,3,5,6,12] Zolpidem ER, eszopiclone, Silenor, and Rozerem are also indicated for the treatment of insomnia, but their product labeling does not specifically limit their use to short-term.[2,4,8,9] All of the agents in this category have been shown to decrease sleep latency. Zaleplon and Rozerem are specifically indicated for the treatment of insomnia characterized by difficulty with sleep onset.[3,8] Zolpidem IR, zolpidem ER, Silenor, and eszopiclone have also been shown to improve sleep maintenance or increase the duration of sleep.[1,2,4,9] Belsomra and Dayvigo are indicated for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.[10,11] Zolpidem sublingual tablets are indicated for use as needed for the treatment of insomnia when a middle-of-the-night (MOTN) awakening is followed by difficulty returning to sleep.[7] However, zolpidem sublingual tablets are not indicated for treatment of MOTN insomnia when the patient has fewer than 4 hours of bedtime remaining before the planned time of waking. Doxepin is also available generically as oral capsules (10, 25, 50, 75, 100, and 150 mg) and oral solution (10 mg/mL).[12] These higher dose formulations are recommended for use in patients with depression and/or anxiety of varying etiologies.

Disease Overview

Insomnia is defined in the International Classification of Sleep Disorders, Third Edition, as a complaint of trouble initiating or maintaining sleep, resulting in daytime consequences (e.g., daytime fatigue, irritability, and decreased concentration) which is not attributable to environmental circumstances or inadequate opportunity for sleep.[13] Specific sleep complaints of patients with insomnia include delayed sleep onset, frequent awakenings, early morning awakenings, and waking up feeling unrefreshed. A wide array of terminology exists for defining the duration of insomnia symptoms. Generally, transient insomnia lasts less than 1 week, short-term (acute) insomnia lasts up to 3 months, and chronic insomnia lasts more than 3 months at a frequency of at least three times per week.[13,14] Symptoms of insomnia commonly wax and wane over time, and manifestations of insomnia often change over time (e.g., difficulty falling to sleep changes to difficulty staying asleep, or vice versa). Insomnia is often subtyped by the predominant symptom, either sleep onset or sleep maintenance.[15]

Guidelines

The American Academy of Sleep Medicine (AASM) published a clinical guideline for the evaluation and management of chronic insomnia in adults (2008).[16] Insomnia is primarily diagnosed by clinical evaluation through a thorough sleep history and detailed medical, substance, and psychiatric history. The evaluation and differential diagnosis of insomnia can be aided by self-administered questionnaires, at-home sleep logs, symptom checklists, psychological

screening tests, and bed partner interviews. At a minimum, patients should complete a general medical/psychiatric questionnaire to identify comorbid disorders; a sleepiness assessment (e.g., Epworth Sleepiness Scale) to identify sleepy patients and comorbid disorders of sleepiness; and a 2-week sleep log to identify general patterns of sleep-wake times and day-to-day variability. A sleep diary should be maintained prior to and during the course of active treatment and in the case of relapse or reevaluation in the long-term. The primary treatment goals are to improve sleep quality and quantity and to improve insomnia related daytime impairments. Initial approaches to treatment should include at least one behavioral intervention such as stimulus control therapy or relaxation therapy, or the combination of cognitive therapy, stimulus control therapy, sleep restriction therapy with or without relaxation therapy. Patients should be instructed to keep a regular schedule; have a healthy diet, regular daytime exercise, and a quiet sleep environment; and avoid napping, caffeine, other stimulants, nicotine, alcohol, excessive fluids, or stimulating activities before bedtime. Short-term hypnotic treatment should be supplemented with behavioral and cognitive therapies when possible. Chronic hypnotic medication may be indicated for long-term use in patients with severe or refractory insomnia or chronic comorbid illness. Whenever possible, patients should receive an adequate trial of cognitive behavioral treatment during long-term pharmacotherapy. Long-term prescribing should be accompanied by regular follow-up, ongoing assessment of effectiveness, monitoring for adverse events, and evaluation for new onset or exacerbation of existing comorbid disorders.

The AASM published an updated clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults (2017).[13] The recommendations are intended as a guide for choosing a specific pharmacological agent (vs. no treatment) for treatment of chronic insomnia in adults, when such treatment is indicated. Each of the recommendations listed is weak, meaning it reflects a lower degree of certainty in the outcome and appropriateness of the patient care strategy for all patients but should not be construed as an indication of ineffectiveness. The guideline suggests that clinicians can use Belsomra as a treatment for sleep maintenance insomnia; eszopiclone can be used as a treatment for sleep onset and sleep maintenance insomnia; zaleplon can be used as a treatment for sleep onset insomnia; zolpidem can be used as a treatment for sleep onset and sleep maintenance insomnia; triazolam can be used as a treatment for sleep onset insomnia; temazepam can be used as a treatment for sleep onset and sleep maintenance insomnia; ramelteon can be used as a treatment for sleep onset insomnia; and Silenor can be used as a treatment for sleep maintenance insomnia. The guideline suggested that clinicians not use trazodone, tiagabine, diphenhydramine, melatonin, tryptophan, or valerian as a treatment for sleep onset or sleep maintenance insomnia. The authors note that cognitive behavioral therapy for insomnia (CBT-I) is a standard of care for this condition; however, the AASM guideline does not address the relative benefits of CBT-I vs. pharmacotherapy.

The American College of Physicians (ACP) developed a guideline on the management of chronic insomnia disorder in adults (2016).[17,18] Chronic insomnia can be managed with psychological therapy, pharmacologic therapy, or a combination of both. Psychological therapy options include CBT-I and other interventions, such as stimulus control, relaxation strategies, and sleep restriction. ACP recommends that all adults receive CBT-I as the initial treatment for chronic insomnia disorder (strong recommendation, moderate-quality evidence). ACP recommends that clinicians use a shared decision-making approach, including a discussion of the benefits, harms, and costs of short-term use of medications, to decide whether to prescribe a medication in adults with chronic insomnia disorder in whom CBT-I alone was unsuccessful (weak recommendation, low-quality evidence). A review of the evidence found that eszopiclone, zolpidem, Belsomra, and Silenor may improve short-term global and sleep outcomes for adults with insomnia disorder (low- to moderate-quality evidence), but the comparative effectiveness and long-term efficacy of pharmacotherapies for insomnia are unknown. ACP also notes that pharmacotherapies for insomnia may cause cognitive and behavioral changes and may be associated with infrequent but serious harms.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of sedative hypnotics. All approvals are provided for the duration noted below.

Automation: Patients who use at least 180 days of a sedative/hypnotic medication in a 365-day time period will require prior authorization. If the patient has a prescription for a cancer medication (see Appendix A) within a 180-day period, the claim will adjudicate. When available, the ICD-10 codes for cancer will be used as part of automation to allow approval of the requested medication (see Appendix B).

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of a sedative hypnotic is recommended in those who meet the following criteria:

FDA-Approved Indications

41. Chronic Insomnia. Approve for 1 year if the patient meets ONE of the following criteria (A or B):

H) The patient has a cancer diagnosis; OR

I) The patient meets ALL of the following criteria (i, ii, iii, and iv):

E) Patient has tried at least one form of behavioral therapy for insomnia; AND

Note: Examples of behavioral therapy for insomnia include relaxation training, stimulus control therapy, or sleep restriction therapy.

F) Patient is not currently taking prescription stimulants (e.g., methylphenidate, amphetamine products); AND

G) Underlying psychiatric and/or medical conditions that may cause or exacerbate insomnia have been evaluated and are currently being addressed, according to the prescriber; AND

H) Patient's sleep quality and quantity and/or insomnia-related daytime impairments continue to improve or remain stable, according to the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Sedative hypnotics have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

247. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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800. Wilt TJ, MacDonald R, Brasure M, et al. Pharmacologic treatment of insomnia disorder: An evidence report for a clinical practice guideline by the American College of Physicians. *Ann Intern Med*. 2016;165(2):103-112.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	05/27/2020

APPENDIX A

Note: This list is not inclusive. As new STCs become available, they will roll into this policy and the list will be updated periodically.

STC*	STC Description
0470	ANTINEOPLASTIC - ALKYLATING AGENTS
0471	ANTINEOPLASTIC - ANTIMETABOLITES
0472	ANTINEOPLASTIC - VINCA ALKALOIDS
0473	ANTIBIOTIC ANTINEOPLASTICS
0475	ANTINEOPLASTICS, MISCELLANEOUS
6323	ANTINEOPLASTIC - ANTIANDROGENIC AGENTS
7235	ANTINEOPLASTICS ANTIBODY/ANTIBODY-DRUG COMPLEXES
7977	ANTINEOPLASTIC IMMUNOMODULATOR AGENTS
8254	ANTINEOPLASTIC LHRH(GNRH) AGONIST, PITUITARY SUPPR.
8460	ANTINEOPLASTIC LHRH(GNRH) ANTAGONIST,PITUIT.SUPPRS
8569	ANTINEOPLASTIC EGF RECEPTOR BLOCKER MCLON ANTIBODY
8585	ANTINEOPLAST HUM VEGF INHIBITOR RECOMB MC ANTIBODY
9150	ANTINEOPLASTIC SYSTEMIC ENZYME INHIBITORS
B759	ANTINEOPLAST, HISTONE DEACETYLASE (HDAC) INHIBITORS
C232	ANTINEOPLASTIC - MTOR KINASE INHIBITORS
C370	ANTINEOPLASTIC - EPOTHILONES AND ANALOGS
C532	ANTINEOPLASTIC - TOPOISOMERASE I INHIBITORS
C593	ANTINEOPLASTIC - AROMATASE INHIBITORS
D426	ANTINEOPLASTIC - IMMUNOTHERAPY, THERAPEUTIC VAC
D560	ANTINEOPLASTIC - HALICHONDRIN B ANALOGS
D687	CYTOTOXIC T-LYMPHOCYTE ANTIGEN (CTLA-4) RMC ANTIBODY
E039	ANTINEOPLASTIC - JANUS KINASE (JAK) INHIBITORS
E150	ANTINEOPLASTIC - HEDGEHOG PATHWAY INHIBITOR
E600	ANTINEOPLASTIC - VEGF-A,B AND PLGF INHIBITORS
F495	ANTINEOPLASTIC - INTERLEUKIN-6(IL-6)INHIB,ANTIBODY
F501	ANTINEOPLASTIC - VEGFR ANTAGONIST
F665	ANTINEOPLASTIC, ANTI-PROGRAMMED DEATH-1 (PD-1) MAB
G545	ANTINEOPLASTIC - IMMUNOTHERAPY, VIRUS-BASED AGENTS
G575	ANTINEOPLASTIC - MEK1 AND MEK2 KINASE INHIBITORS
G590	ANTINEOPLASTIC - ANTI-CD38 MONOCLONAL ANTIBODY
G607	ANTINEOPLASTIC - ANTI-SLAMF7 MONOCLONAL ANTIBODY
G802	ANTINEOPLASTIC- B CELL LYMPHOMA-2(BCL-2) INHIBITORS
G857	ANTI-PROGRAMMED CELL DEATH-LIGAND 1 (PD-L1) MAB
H018	ANTINEOPLASTIC, PDGFR-ALPHA BLOCKER MC ANTIBODY
H214	ANTINEOPLASTIC COMB-KINASE AND AROMATASE INHIBIT
H289	ANTINEOPLASTIC-ISOCITRATE DEHYDROGENASE INHIBITORS
H309	ANTINEOPLASTIC – ANTIBIOTIC AND ANTIMETABOLITE
H317	ANTINEOPLASTIC – CD22 ANTIBODY-CYTOTOXIC ANTIBIOTIC
H324	ANTINEOPLASTIC- CD19 DIR. CAR-T CELL IMMUNOTHERAPY
H329	ANTINEOPLASTIC – CD33 ANTIBODY-CYTOTOXIC ANTIBIOTIC
H617	ANTINEOPLASTIC – BRAF KINASE INHIBITORS
H768	ANTINEOPLASTIC-CD22 DIRECT ANTIBODY/CYTOTOXIN CONJ
H868	ANTINEOPLASTIC-CD123-DIRECTED CYTOTOXIN CONJUGATE
I054	ANTINEOPLASTIC-SELECT INHIB OF NUCLEAR EXP (SINE)
I264	ANTINEOPLASTIC – PROTEIN METHYLTRANSFERASE INHIBITORS

* Excluding topical products

APPENDIX B

ICD-10 Codes

Cancer-related codes
C00.* to D09.*
D3A.* to D48.*
E34.0*
Q85.0*

*Indicates the inclusion of subheadings.

PRIOR AUTHORIZATION POLICY

POLICY: Sickle Cell Disease – Adakveo Prior Authorization Policy

- Adakveo® (crizanlizumab-tmca injection, for intravenous use – Novartis)

REVIEW DATE: 12/02/2020

OVERVIEW

Adakveo, a monoclonal antibody, is indicated to **reduce the frequency of vasocclusive crises** in patients aged 16 years and older with **sickle cell disease**.[1]

DISEASE OVERVIEW

Sickle cell disease, a multisystem disorder, is the most common condition caused by a single gene mutation.[2] In the US, population estimates suggest that a total of 100,000 persons have the disease. Approximately 300,000 babies are born with sickle cell anemia each year and it is estimated that the number could be as high as 400,000 by 2050.

Sickle cell disease is characterized by the presence of abnormal erythrocytes damaged by the sickle hemoglobin gene – this variant of the normal adult hemoglobin can be inherited from both parents or from one parent along with another variant, such as hemoglobin C or with β-thalassemia.[2] Complications of sickle cell disease include vaso-occlusion (which can result in pain and organ failure), hemolytic anemia, and large-vessel vasculopathy (cerebrovascular disease, pulmonary hypertension, ischemic organ damage hyposplenism, renal failure, bone disease, liver failure).

Guidelines

Adakveo has not been added to guidelines. The National Institutes of Health – National Heart, Lung, and Blood Institute issued the Evidence-Based Management of Sickle Cell Disease, Expert Panel Report in 2014.[3] There are two effective disease-modifying therapies for sickle cell disease: hydroxyurea and chronic blood transfusions. Hydroxyurea has been shown to reduce: the frequency of painful episodes, incidence of acute coronary syndrome events, and the need for transfusions and hospitalizations.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Adakveo. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Adakveo as well as the monitoring required for adverse events and long-term efficacy, approval requires Adakveo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Adakveo is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Sickle Cell Disease.** Approve for 1 year if the patient meets ONE of the following criteria (A or B):
   - **A)** Initial Therapy. Approve if the patient meets ALL of the following criteria (i, ii, iii, and iv):
     - **i.** Patient is ≥ 16 years of age; AND
     - **ii.** Patient has had at least one sickle-cell related crisis in the previous 12-month period; AND
     - **iii.** Patient meets one of the following criteria (a, b, or c):
       - **a.** Patient is currently receiving a hydroxyurea product; OR
       - **b.** According to the prescriber, patient has tried a hydroxyurea product and has experienced inadequate efficacy or significant intolerance; OR
       - **c.** According to the prescriber, patient is not a candidate for hydroxyurea therapy; AND
         Note: Examples of patients who are not candidates for hydroxyurea therapy include patients who are pregnant or who are planning to become pregnant and patients with an immunosuppressive condition (such as cancer).
     - **iv.** The medication is prescribed by or in consultation with a physician who specializes in sickle cell disease (e.g., a hematologist).
   - **B)** Patient is Currently Receiving Adakveo. Approve for 1 year if the patient meets ALL of the following criteria (i, ii, and iii):
     - ~~**84.**~~**81.** Patient is ≥ 16 years of age; AND
     - ~~**85.**~~**82.** According to the prescriber, patient is receiving clinical benefit from Adakveo therapy; AND
       Note: Examples of clinical benefit include reduction in the number of vaso-occlusive crises/sickle cell-related crises; delay in time to sickle cell-related crises; and reduction in the number of days in the hospital.
     - ~~**86.**~~**83.** The medication is prescribed by or in consultation with a physician who specializes in sickle cell disease (e.g., a hematologist).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Adakveo is not recommended in the following situations:

248. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

376. Adakveo® injection for intravenous use [prescribing information]. East Hanover, NJ: Novartis; November 2019.
377. Piel FB, Steinberg MH. Sickle cell disease. *N Engl J Med*. 2017;376:1561-1573.
378. The National Institutes of Health – National Heart, Lung, and Blood Institute Evidence-Based Management of Sickle Cell Disease, Expert Panel Report 2014. Available at: https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf . Accessed on October 27, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	11/20/2019
Update	12/04/2019: Changed name of policy from "Hematology – Adakveo PA" to "Sickle Cell Disease – Adakveo PA".	NA
Annual Revision	The criteria were separated as two sets, one for Initial Therapy and one for a Patient Currently Receiving Therapy. • For Initial Therapy, it was added that the patient has a history of at least one sickle cell-related crisis in the previous 12-month period. Also, a patient must currently be receiving a hydroxyurea product; or the patient has tried a hydroxyurea product and has experienced inadequate efficacy or significant intolerance, according to the prescriber; or the patient is not a candidate for hydroxyurea therapy, according to the prescriber. A Note was added citing examples of patients who are not candidates for hydroxyurea therapy. • For a patient Currently Receiving Adakveo, criteria were added to approve for 1 year if the patient meets all of the following: patient is ≥ 16 years of age; patient is receiving clinical benefit, according to the prescriber; and the medication is prescribed by or in consultation with a physician who specializes in sickle cell disease (e.g., a hematologist). Also, examples of clinical benefit were provided in a Note.	12/02/2020

NA – Not applicable.

PRIOR AUTHORIZATION POLICY

POLICY: Sickle Cell Disease – Endari Prior Authorization Policy
- Endari™ (L-glutamine oral powder – Emmaus Medical)

REVIEW DATE: 11/11/2020

OVERVIEW

Endari is indicated to **reduce the acute complications of sickle cell disease** in adults and pediatric patients ≥ 5 years of age.[1]

L-glutamine is an essential amino acid and serves as a precursor of nucleic acids and nucleotides including the pyridine nucleotides (nicotinamide adenine dinucleotide and reduced nicotinamide adenine dinucleotide).[1,2] These pyridine nucleotides play key roles in the regulation and prevention of oxidative damage in red blood cells and studies have shown that oxidative phenomena may play a significant role in the pathophysiology of sickle cell disease.

Disease Overview

Sickle cell disease, a multisystem disorder, is the most common condition caused by a single gene mutation.[3] In the US, population estimates suggest that a total of 100,000 persons have the disease. Approximately 300,000 babies are born with sickle cell anemia each year and it is estimated that the number could be as high as 400,000 by 2050.

Sickle cell disease is characterized by the presence of abnormal erythrocytes damaged by the sickle hemoglobin gene – this variant of the normal adult hemoglobin can be inherited from both parents or from one parent along with another variant, such as hemoglobin C or with β-thalassemia.[3] Complications of sickle cell disease include vaso-occlusion (which can result in pain and organ failure), hemolytic anemia, and large-vessel vasculopathy (cerebrovascular disease, pulmonary hypertension, ischemic organ damage, hyposplenism, renal failure, bone disease, liver failure).

Guidelines

The National Institutes of Health – National Heart, Lung, and Blood Institute issued the Evidence-Based Management of Sickle Cell Disease, Expert Panel Report in 2014.[4] The use of L-glutamine products in sickle cell disease is not mentioned (guidelines were published before the approval of Endari). Hydroxyurea has been shown to reduce the frequency of painful episodes and acute coronary syndrome events and reduce the need for transfusions and hospitalizations.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Endari. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Endari as well as the monitoring required for adverse events and long-term efficacy, approval requires Endari to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Endari as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Endari is recommended in those who meet the following criteria:

FDA-Approved Indication

~~87.~~84. **Sickle Cell Disease [documentation required].** Approve for 1 year if the patient meets the following criteria (A and B):

B) Patient is ≥ 5 years of age; AND

C) The medication is prescribed by or in consultation with a physician who specializes in sickle cell disease (e.g., a hematologist).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Endari is not recommended in the following situations:

314. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

379. Endari™ oral powder [prescribing information]. Torrance CA: Emmaus Medical, Inc; November 2019.
380. FDA Briefing document, Oncologic Drugs Advisory Committee Meeting: L-glutamine. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM559734.pdf. Accessed on October 22, 2020.
381. Piel FB, Steinberg MH. Sickle cell disease. *N Engl J Med*. 2017;376:1561-1573.
382. The National Institutes of Health – National Heart, Lung, and Blood Institute Evidence-Based Management of Sickle Cell Disease, Expert Panel Report 2014. Available at: https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf. Accessed on October 22, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Selected Revision	Added "documentation required" for the sickle cell disease diagnosis.	04/18/2018
Annual Revision	No criteria changes.	10/17/2018
Annual Revision	No criteria changes.	10/23/2019
Update	10/20/2019: Changed name of policy from "Endari PA" to "Hematology – Endari PA".	NA
Update	12/04/2019: Changed name of policy from "Hematology – Endari PA" to "Sickle Cell Disease – Endari PA".	NA
Annual Revision	No criteria changes.	11/11/2020

NA – Not applicable.

PRIOR AUTHORIZATION POLICY

POLICY: Sickle Cell Disease – Oxbryta Prior Authorization Policy

- Oxbryta™ (voxelotor tablets – Global Blood Therapeutics)

REVIEW DATE: 12/02/2020

OVERVIEW

Oxbryta, a hemoglobin S (or sickle hemoglobin) polymerization inhibitor, is indicated for the **treatment of sickle cell disease** in adults and pediatric patients 12 years of age and older.[1]

Disease Overview

Sickle cell disease, a multisystem disorder, is the most common condition caused by a single gene mutation.[2] In the US, population estimates suggest 100,000 persons have the disease. Approximately 300,000 babies are born with sickle cell anemia each year and it is estimated that the number could be as high as 400,000 by 2050.

Sickle cell disease is characterized by the presence of abnormal erythrocytes damaged by the sickle hemoglobin gene – this variant of the normal adult hemoglobin can be inherited from both parents or from one parent along with another variant, such as hemoglobin C or with β-thalassemia.[2] Complications of sickle cell disease include vaso-occlusion (which can result in pain and organ failure), hemolytic anemia, and large-vessel vasculopathy (cerebrovascular disease, pulmonary hypertension, ischemic organ damage, hyposplenism, renal failure, bone disease, liver failure).

Guidelines

Oxbryta has not been added to guidelines. The National Institutes of Health – National Heart, Lung, and Blood Institute issued the Evidence-Based Management of Sickle Cell Disease, Expert Panel Report in 2014.[3] There are two effective disease-modifying treatments for sickle cell disease: hydroxyurea and chronic blood transfusions. Hydroxyurea has been shown to reduce: the frequency of painful episodes, incidence of acute coronary syndrome events, and the need for transfusions and hospitalizations.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Oxbryta. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Oxbryta as well as the monitoring required for adverse events and long-term efficacy, approval requires Oxbryta to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Oxbryta is recommended in those who meet the following criteria:

FDA-Approved Indication

~~88.~~85. **Sickle Cell Disease.** Approve for 1 year if the patient meets ONE of the following criteria (A or B):

D) Initial Therapy. Approve if the patient meets ALL of the following criteria (i, ii, iii, iv and v):
- **i.** Patient is ≥ 12 years of age; AND
- **ii.** Patient has had at least one sickle cell-related crisis in the previous 12-month period; AND
- **iii.** Patient's baseline hemoglobin level was ≤ 10.5 g/dL (before initiating Oxbryta therapy); AND
- **iv.** Patient meets one of the following criteria (a, b, or c):
  - **a.** Patient is currently receiving a hydroxyurea product; OR
  - **b.** According to the prescriber, patient has tried a hydroxyurea product and has experienced inadequate efficacy or significant intolerance; OR
  - **c.** According to the prescriber, patient is not a candidate for hydroxyurea therapy; AND
    Note: Examples of patients who are not candidates for hydroxyurea therapy include patients who are pregnant or who are planning to become pregnant and patients with an immunosuppressive condition (such as cancer).
- **v.** The medication is prescribed by or in consultation with a physician who specializes in sickle cell disease (e.g., a hematologist).

B) Patient is Currently Receiving Oxbryta. Approve for 1 year if the patient meets ALL of the following criteria (i, ii, and iii):
- **i.** Patient is ≥ 12 years of age; AND
- **ii.** According to the prescriber, patient is receiving clinical benefit from Oxbryta therapy; AND
  Note: Examples of clinical benefit include reduction in the number of vaso-occlusive crises/sickle cell-related crises, delay in time to sickle cell-related crises; and reduction in the number of days in the hospital.
- **iii.** The medication is prescribed by or in consultation with a physician who specializes in sickle cell disease (e.g., a hematologist).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Oxbryta is not recommended in the following situations:

249. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

383. Oxbryta™ [prescribing information]. San Francisco, CA: Global Blood Therapeutics; November 2019.
384. Piel FB, Steinberg MH. Sickle cell disease. *N Engl J Med*. 2017;376:1561-1573.
385. The National Institutes of Health – National Heart, Lung, and Blood Institute Evidence-Based Management of Sickle Cell Disease, Expert Panel Report 2014. Available at: https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf Accessed on November 10, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/04/2019
Annual Revision	The criteria were separated as two sets, one for Initial Therapy and one for a Patient Currently Receiving Therapy. • For Initial Therapy, it was added that the patient has a history of at least one sickle cell-related crisis in the previous 12-month period and has a baseline hemoglobin level ≤ 10.5 g/dL. Also, that patient must currently be receiving a hydroxyurea product; or the patient has tried a hydroxyurea product and has experienced inadequate efficacy or significant intolerance, according to the prescriber; or the patient is not a candidate for hydroxyurea therapy, according to the prescriber. A Note was added citing examples of patients who are not candidates for hydroxyurea therapy. • For a patient Currently Receiving Oxbryta, criteria were added to approve for 1 year if the patient meets all of the following: patient is ≥ 12 years of age; patient is receiving clinical benefit, according to the prescriber; and the medication is prescribed by or in consultation with a physician who specializes in sickle cell disease (e.g., a hematologist). Also, examples of clinical benefit were provided in a Note.	12/02/2020

PRIOR AUTHORIZATION POLICY

POLICY: Somatostatin Analogs – Mycapssa Prior Authorization Policy

- Mycapssa® (octreotide delayed-release capsules – Chisama)

REVIEW DATE: 09/02/2020

OVERVIEW

Mycapssa, a somatostatin analog, is indicated for long-term maintenance treatment in acromegaly patients who have responded to and tolerated treatment with octreotide or lanreotide.[1] Mycapssa maintained growth hormone and insulin-like growth factor 1 levels in patients with acromegaly.

GUIDELINES

The Endocrine Society Clinical Practice Guidelines for Acromegaly (2014) recommend medical therapy as adjuvant treatment after surgical intervention.[2] Mycapssa is not addressed in the guidelines. Primary medical therapy with somatostatin analogs (no preferred agent) can be recommended for some patients (e.g., surgery is not curative or patient is a poor surgical candidate). Updated recommendations to the 2014 guidelines on therapeutic outcomes for patients with acromegaly were created by the Acromegaly Consensus Group (2017).[3] The statement recommends Somatuline Depot and Sandostatin LAR Depot as first-line medical therapies in patients with persistent disease after surgery. Signifor LAR is recommended as a second-line medical therapy due to its potential for hyperglycemic-associated adverse events.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Mycapssa. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Mycapssa as well as the monitoring required for adverse events and long-term efficacy, approval requires Mycapssa to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mycapssa is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Acromegaly.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** Patient has (or had) a pre-treatment (baseline) insulin-like growth factor 1 (IGF-1) level above the upper limit of normal based on age and gender for the reporting laboratory; AND
     Note: Pre-treatment (baseline) refers to the IGF-1 level prior to the initiation of a somatostatin analog (e.g., Mycapssa® [octreotide delayed-release capsules], an octreotide acetate injection product [e.g., Bynfezia Pen™, Sandostatin® {generics}, Sandostatin® LAR Depot], Signifor® LAR [pasireotide injection], Somatuline® Depot [lanreotide injection], dopamine agonist [e.g., cabergoline, bromocriptine], or Somavert® [pegvisomant injection]). Reference ranges for IGF-1 vary among laboratories.
   - **B)** According to the prescriber, patient has responded to one octreotide acetate injection product or Somatuline® Depot (lanreotide injection); AND
   - **C)** The medication is prescribed by or in consultation with an endocrinologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Mycapssa is not recommended in the following situations:

250. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

386. Mycapssa capsules [prescribing information]. Needham, MA: Chiasma; April 2019.
387. Katznelson L, Laws ER Jr, Melmed S, et al; Endocrine Society. Acromegaly: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2014;99:3933-3951.
388. Melmed S, Bronstein M, Chanson P, et al. A consensus statement on acromegaly therapeutic outcomes. *Natural Reviews Endocrinology.* 2018;14(9):552-561.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	09/02/2020

PRIOR AUTHORIZATION POLICY

POLICY: Somatostatin Analogs – Sandostatin® LAR Depot Prior Authorization Policy

- Sandostatin® LAR Depot (octreotide acetate for injectable suspension – Novartis)

REVIEW DATE: 08/05/2020

OVERVIEW

Sandostatin LAR Depot, a somatostatin analog, is indicated for the following uses:[1]

- **Acromegaly**, in patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy, is not an option. The goal of treatment in acromegaly is to reduce growth hormone and insulin-like growth factor-1 levels to normal.
- **Carcinoid tumors**, in patients with severe diarrhea and flushing episodes associated with metastatic carcinoid tumors.
- **Vasoactive intestinal peptide tumors (VIPomas)**, in patients with profuse watery diarrhea associated with vasoactive intestinal peptide (VIP)-secreting tumors.

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines support use of Sandostatin LAR Depot in multiple conditions.

- **Central Nervous System Cancers:** Guidelines (version 2.2020 – April 30, 2020) recommend Sandostatin LAR Depot for the treatment of meningiomas that recur despite surgery and/or radiation therapy, or are not amenable to treatment with surgery or radiation therapy.[2]
- **Neuroendocrine and Adrenal Tumors:** Guidelines (version 1.2020 – July 10, 2020) recommend Sandostatin LAR Depot for the management of carcinoid syndrome, tumors of the gastrointestinal tract, lung, thymus (carcinoid tumors), and pancreas (including glucagonomas, gastrinomas, VIPomas, insulinomas), pheochromocytomas, and paragangliomas.[3] Patients who have local unresectable disease and/or distant metastases and clinically significant tumor burden or progression should be started on therapy with a somatostatin analog to potentially control tumor growth. The North American Neuroendocrine Tumor Society (NANETS) consensus guidelines for the surveillance and medical management of midgut NETs (2017) also recommend Sandostatin LAR Depot as a first-line initial therapy in most patients with metastatic midgut NETs for control of carcinoid syndrome and inhibition of tumor growth.[4]
- **Thymomas and Thymic Carcinomas:** Guidelines (version 1.2020 – November 27, 2019) recommend Sandostatin LAR Depot as a second-line systemic therapy option with or without concomitant prednisone therapy.[5] In patients with thymoma who have positive octreotide scan or symptoms of carcinoid syndrome, octreotide therapy may be useful.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Sandostatin LAR Depot. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Sandostatin LAR Depot as well as the monitoring required for adverse events and long-term efficacy, approval requires Sandostatin LAR Depot to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sandostatin LAR Depot is recommended in those who meet the following criteria:

FDA-Approved Indications

2. Acromegaly. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **D)** Patient meets ONE of the following (i, ii, or iii):
  - **i.** Patient has had an inadequate response to surgery and/or radiotherapy; OR
  - **ii.** Patient is NOT an appropriate candidate for surgery and/or radiotherapy; OR
  - **iii.** Patient is experiencing negative effects due to tumor size (e.g., optic nerve compression); AND
- **E)** Patient has (or had) a pre-treatment (baseline) insulin-like growth factor-1 (IGF-1) level above the upper limit of normal based on age and gender for the reporting laboratory; AND
  Note: Pre-treatment (baseline) refers to the IGF-1 level prior to the initiation of any somatostatin analog (e.g., Mycapssa® [octreotide delayed-release capsules], an octreotide acetate injection product [e.g., Bynfezia Pen™, Sandostatin® {generics}, Sandostatin® LAR Depot], Signifor® LAR [pasireotide injection], Somatuline® Depot [lanreotide injection], dopamine agonist [e.g., cabergoline, bromocriptine], or Somavert® [pegvisomant injection]). Reference ranges for IGF-1 vary among laboratories.
- **F)** The medication is prescribed by or in consultation with an endocrinologist.

2. Neuroendocrine Tumor(s) [NETs] of the Gastrointestinal Tract, Lung, Thymus (Carcinoid Tumors), and Pancreas (including glucagonomas, gastrinomas, vasoactive intestinal peptides-secreting tumors [VIPomas], insulinomas). Approve for 1 year if the medication is prescribed by or in consultation with an oncologist, endocrinologist, or gastroenterologist.

Other Uses with Supportive Evidence

~~89.~~**86. Meningioma.** Approve for 1 year if the medication is prescribed by or in consultation with an oncologist, radiologist, or neurosurgeon.

~~90.~~**87. Thymoma and Thymic Carcinoma.** Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

~~91.~~**88. Pheochromocytoma and Paraganglioma.** Approve for 1 year if the medication is prescribed by or in consultation with an endocrinologist, oncologist, or neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sandostatin LAR Depot is not recommended in the following situations:

251. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

389. Sandostatin® LAR Depot for injectable suspension [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; April 2019.
390. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 2.2020 – April 30, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed July 16, 2020.
391. The NCCN Neuroendocrine and Adrenal Tumors Clinical Practice Guidelines in Oncology (version 1.2020 – July 10, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed July 16, 2020.
392. Strosberg JR, Halfdanarson TR, Bellizi AR, et al. The North American Neuroendocrine Tumor Society consensus guidelines for surveillance and medical management of midgut neuroendocrine Tumors. *Pancreas*. 2017;46(6):707-714.
393. The NCCN Thymomas and Thymic Carcinomas Clinical Practice Guidelines in Oncology (version 1.2020 – July 10, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed July 16, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	Added more specific conditions to the indication: "Neuroendocrine Tumor(s) [NETs] of the Gastrointestinal Tract, Lung, Thymus (Carcinoid Tumors), and Pancreas (including glucagonomas, gastrinomas, vasoactive intestinal peptides-secreting tumors [VIPomas], insulinomas)". Deleted "Note" that described the different types of neuroendocrine tumors since now it's in the approval condition. Also added criteria requiring specialist physician for NETs, meningiomas, and thymic carcinoma indications. Changed approval duration from 3 years to 1 year.	08/22/2018
Annual revision	Addition of indication for pheochromocytoma/paraganglioma to approval criteria.	07/31/2019
Annual Revision	**Acromegaly.** In the Note section referring to the pre-treatment (baseline) insulin-like growth factor-1 (IGF-1) level, Mycapssa® (octreotide delayed-release capsules) and octreotide acetate injection products (Bynfezia Pen™, Sandostatin® [generics]) were added as examples of a somatostatin analog.	08/05/2020

PRIOR AUTHORIZATION POLICY

POLICY: Somatostatin Analogs – Signifor LAR Prior Authorization Policy

- Signifor® LAR (pasireotide injectable suspension – Recordati Rare Diseases)

REVIEW DATE: 08/05/2020

OVERVIEW

Signifor LAR, a somatostatin analog, is indicated for the following uses:[1]

- **Acromegaly**, in patients who have had an inadequate response to surgery and/or for whom surgery is not an option. In vivo studies show that Signifor LAR lowers growth hormone and insulin-like growth factor-1 levels in patients with acromegaly.
- **Cushing's disease**, in patients for whom pituitary surgery is not an option or has not been curative.

Cushing's Syndrome/Disease

Cushing's syndrome refers to the general state of excessive levels of cortisol (hypercortisolism) in the blood.[2,3] Hypercortisolism can occur for reasons that are either endogenous or exogenous in nature (e.g., Cushing's disease, cortisol-containing medications, adrenal gland tumor, certain cancers). Endogenous Cushing's syndrome can be divided into adrenocorticotropic hormone (ACTH)-dependent and ACTH-independent, with the majority of cases

being ACTH-dependent (80%). Cushing's disease (hypercortisolism caused by pituitary adenomas) is the most common type of ACTH-dependent Cushing's syndrome. Treatment for Cushing's syndrome requires a multi-modal approach. The goals of treatment are normalization of cortisol excess, long-term disease control, avoidance of recurrence, and reversal of clinical features.[4]

Guidelines

The Endocrine Society published clinical practice guidelines (2015) for the treatment of Cushing's syndrome.[5] Signifor LAR is not addressed in the guidelines. Treatment goals for Cushing's syndrome are to normalize cortisol levels or its action at the receptors to eliminate signs and symptoms of Cushing's syndrome. Best practice adjunctive management includes treating comorbidities associated with hypercortisolism (psychiatric disorders, diabetes, hypertension, hypokalemia, infections, dyslipidemia, osteoporosis, and poor physical fitness). First-line treatment involves resection of the tumor, unless surgery is not possible or is unlikely to meaningfully reduce excess glucocorticoid levels. Specifically for Cushing's disease, transsphenoidal selective adenomectomy by a surgeon with extensive experience in pituitary surgery is recommended. In patients with ACTH-dependent Cushing's syndrome who underwent non-curative surgery or for whom surgery was not possible, the guidelines advocate several second-line therapies (e.g., repeat transsphenoidal surgery, radiotherapy, medical therapy, and bilateral adrenalectomy). For Cushing's disease, the guidelines recommend all medical therapies as second-line options after transsphenoidal surgery: steroidogenesis inhibitors (ketoconazole, Metopirone, Lysodren, etomidate) in patients either with or without radiotherapy/radiosurgery; pituitary-directed medical treatments (cabergoline, Signifor) in patients who are not surgical candidates or who have persistent disease; and Korlym in patients with diabetes or glucose intolerance who are not surgical candidates or who have persistent disease after transsphenoidal surgery.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Signifor LAR. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Signifor LAR as well as the monitoring required for adverse events and long-term efficacy, approval requires Signifor LAR to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Signifor LAR is recommended in those who meet the following criteria:

FDA-Approved Indications

3. Acromegaly. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **G)** Patient meets ONE of the following (i, ii, or iii):
  - **i.** Patient has had an inadequate response to surgery and/or radiotherapy; OR
  - **ii.** Patient is NOT an appropriate candidate for surgery and/or radiotherapy; OR
  - **iii.** Patient is experiencing negative effects due to tumor size (e.g., optic nerve compression); AND
- **H)** Patient has (or had) a pre-treatment (baseline) insulin-like growth factor-1 (IGF-1) level above the upper limit of normal based on age and gender for the reporting laboratory; AND
  Note: Pre-treatment (baseline) refers to the IGF-1 level prior to the initiation of any somatostatin analog (e.g., Mycapssa® [octreotide delayed-release capsules], an octreotide acetate injection product [e.g., Bynfezia Pen™, Sandostatin® {generics}, Sandostatin® LAR Depot], Signifor® LAR [pasireotide injection], Somatuline® Depot [lanreotide injection], dopamine agonist [e.g., cabergoline, bromocriptine], or Somavert® [pegvisomant for injection]). Reference ranges for IGF-1 vary among laboratories.
- **I)** The medication is prescribed by or in consultation with an endocrinologist.

2. Cushing's Disease. Approve for the duration noted if the patient meets the following criteria (A or B):
- **A)** Initial Therapy. Approve for 4 months of initial therapy if the patient meets the following criteria (i and ii):
  - **i.** According to the prescriber, patient is not a candidate for surgery, or surgery has not been curative; AND
    Note: For patients with Cushing's disease/syndrome awaiting surgery, see *Other Uses with Supportive Evidence.*
  - **ii.** Signifor LAR is prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of Cushing's disease.
- **B)** Patient is Currently Receiving Signifor LAR/Signifor. Approve for 1 year of continuation therapy if the patient has responded to Signifor/Signifor LAR, as determined by the prescriber.
  Note: An example of patient response is decrease in the mean urinary free cortisol level.

Other Uses with Supportive Evidence

3. **Cushing's Disease/Syndrome – Patients Awaiting Surgery.** Approve for 4 months if Signifor LAR is prescribed by or in consultation with an endocrinologist or a physician who specialized in the treatment of Cushing's disease/syndrome.

4. **Cushing's Disease/Syndrome – Patients Awaiting Therapeutic Response After Radiotherapy.** Approve for 4 months if Signifor LAR is prescribed by or in consultation with an endocrinologist or a physician who specialized in the treatment of Cushing's disease/syndrome.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Signifor LAR is not recommended in the following situations:

252. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

394. Signifor® LAR injectable suspension [prescribing information]. Lebanon, NJ: Recordati Rare Diseases; March 2020.
395. Sharma ST, Nieman LK, Feelders RA. Cushing's syndrome: epidemiology and developments in disease management. *Clin Epidemiol*. 2015;7:281–293.
396. Tritos NA, Biller BM. Advances in medical therapies for Cushing's syndrome. *Discov Med*. 2012;13(69):171-179.
397. Biller BMK, Grossman AB, Stewart PM, et al. Treatment of adrenocorticotropin-dependent Cushing's syndrome: A consensus statement. *J Clin Endocrinol Metab*. 2008;93:2454-2462.
398. Nieman LK, Biller BM, Findling JW. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2015;100(8):2807-2831.

HISTORY

Type of Revision	Summary of Changes	Review Date
Selected Revision	Criteria created for the following FDA-approved diagnosis: Patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative. Criteria created for Other Uses with Supportive Evidence: Cushing's disease, awaiting surgery.	08/01/2018
Annual Revision	Specified Cushing's Disease/"Syndrome" to approval condition and added "Patients" awaiting surgery. Approval duration increased from 2 months to 4 months to align. Created separate approval condition for Cushing's Disease/Syndrome – Patients Awaiting Therapeutic Response from Radiotherapy with 4 month approval duration. Initial therapy approval criteria for Cushing's Disease changed to 4 months.	08/22/2018
Annual Revision	No criteria changes.	07/31/2019
Annual Revision	**Acromegaly.** In the Note section referring to the pre-treatment (baseline) insulin-like growth factor-1 (IGF-1) level, Mycapssa® (octreotide delayed-release capsules) and octreotide acetate injection products (Bynfezia Pen™, Sandostatin® [generics]) were added as examples of a somatostatin analog. **Cushing's Disease.** For the exception applying to a patient who is not a candidate for surgery or surgery has not been curative, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician).	08/05/2020

PRIOR AUTHORIZATION POLICY

POLICY: Somatostatin Analogs – Somatuline® Depot Prior Authorization Policy

- Somatuline Depot (lanreotide injection – Ipsen)

REVIEW DATE: 08/05/2020

OVERVIEW

Somatuline Depot, a somatostatin analog, is indicated for the following uses:[1]

- **Acromegaly**, in patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy, is not an option. The goal of treatment in acromegaly is to reduce growth hormone and insulin-like growth factor-1 levels to normal.
- **Carcinoid syndrome**, in adult patients.
- **Gastroenteropancreatic neuroendocrine tumors (GEP-NETs)**, in adult patients with unresectable, well or moderately differentiated, locally advanced or metastatic GEP-NETs to improve progression-free survival.

Guidelines

According to the National Comprehensive Cancer Network (NCCN) guidelines for neuroendocrine and adrenal tumors (version 1.2020 – July 10, 2020) recommend Somatuline Depot for the management of carcinoid syndrome, tumors of the gastrointestinal tract, lung, thymus (carcinoid tumors), and pancreas (including glucagonomas, gastrinomas, VIPomas, insulinomas), pheochromocytomas and paragangliomas.[2] Patients who have local unresectable disease and/or distant metastases and clinically significant tumor burden or progression should be started on therapy with a somatostatin analog to potentially control tumor growth.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Somatuline Depot. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Somatuline Depot as well as the monitoring required for adverse events and long-term efficacy, approval requires Somatuline Depot to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Somatuline Depot is recommended in those who meet the following criteria:

FDA-Approved Indications

4. Acromegaly. Approve for 1 year if the patient meets the following criteria (A, B, and C):

A) Patient meets ONE of the following (i, ii, or iii):

i. Patient has had an inadequate response to surgery and/or radiotherapy; OR

ii. Patient is NOT an appropriate candidate for surgery and/or radiotherapy; OR

iii. Patient is experiencing negative effects due to tumor size (e.g., optic nerve compression); AND

B) Patient has (or had) a pre-treatment (baseline) insulin-like growth factor-1 (IGF-1) level above the upper limit of normal (ULN) based on age and gender for the reporting laboratory; AND

Note: Pre-treatment (baseline) refers to the IGF-1 level prior to the initiation of any somatostatin analog (e.g., Mycapssa® [octreotide delayed-release capsules], an octreotide acetate injection product [e.g., Bynfezia Pen™, Sandostatin® {generics}, Sandostatin® LAR Depot], Signifor® LAR [pasireotide injection], Somatuline® Depot [lanreotide injection], dopamine agonist [e.g., cabergoline, bromocriptine], or Somavert® [pegvisomant injection]). Reference ranges for IGF-1 vary among laboratories.

C) The medication is prescribed by or in consultation with an endocrinologist.

2. Neuroendocrine Tumor(s) [NETs] of the Gastrointestinal Tract, Lung, Thymus (Carcinoid Tumors), and Pancreas (including glucagonomas, gastrinomas, vasoactive intestinal peptides-secreting tumors [VIPomas], insulinomas). Approve for 1 year if the medication is prescribed by or in consultation with an oncologist, endocrinologist, or gastroenterologist.

~~92.~~89. **Carcinoid Syndrome.** Approve for 1 year if the medication is prescribed by or in consultation with an oncologist, endocrinologist, or gastroenterologist.

Other Uses with Supportive Evidence

~~93.~~90. **Pheochromocytoma and Paraganglioma.** Approve for 1 year if the medication is prescribed by or in consultation with an endocrinologist, oncologist, or neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Somatuline Depot is not recommended in the following situations:

253. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

399. Somatuline® Depot injection [prescribing information]. Basking Ridge, NJ: Ipsen Biopharmaceuticals, Inc.; April 2019.
400. The NCCN Neuroendocrine and Adrenal Tumors Clinical Practice Guidelines in Oncology (version 1.2020 – July 10, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed July 16, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Added more specific conditions to the indication: "Neuroendocrine Tumor(s) [NETs] of the Gastrointestinal Tract, Lung, Thymus (Carcinoid Tumors), and Pancreas (including glucagonomas, gastrinomas, vasoactive intestinal peptides-secreting tumors [VIPomas], insulinomas)". Deleted "Note" since now it is in the approval condition. Also added criteria requiring specialist physician for neuroendocrine tumors and carcinoid syndrome indications. Changed approval duration from 3 years to 1 year for neuroendocrine tumors and carcinoid syndrome indications.	08/22/2018
Annual Revision	Addition of indication for pheochromocytoma/paraganglioma to approval criteria.	07/31/2019
Annual Revision	**Acromegaly.** In the Note section referring to the pre-treatment (baseline) insulin-like growth factor-1 (IGF-1) level, Mycapssa® (octreotide delayed-release capsules) and octreotide acetate injection products (Bynfezia Pen™, Sandostatin® [generics]) were added as examples of a somatostatin analog.	08/05/2020

PRIOR AUTHORIZATION POLICY

POLICY: Somavert Prior Authorization Policy

- Somavert® (pegvisomant for injection – Pfizer)

REVIEW DATE: 08/05/2020

OVERVIEW

Somavert, a growth hormone-receptor antagonist, is indicated for the treatment of acromegaly in patients who have had inadequate response to surgery and/or radiation therapy and/or other medical therapies, or for whom these therapies are not appropriate.[1] The goal of treatment is to normalize serum insulin-like growth factor-I levels.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Somavert. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Somavert as well as the monitoring required for adverse events and long-term efficacy, approval requires Somavert to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Somavert is recommended in those who meet the following criteria:

FDA-Approved Indications

5. Acromegaly. Approve for 1 year if the patient meets the following criteria (A, B, and C):

J) Patient meets ONE of the following (i, ii, or iii):

i. Patient has had an inadequate response to surgery and/or radiotherapy; OR

ii. Patient is NOT an appropriate candidate for surgery and/or radiotherapy; OR

iii. Patient is experiencing negative effects due to tumor size (e.g., optic nerve compression); AND

K) Patient has (or had) a pre-treatment (baseline) insulin-like growth factor-1 (IGF-1) level above the upper limit of normal (ULN) based on age and gender for the reporting laboratory; AND

Note: Pre-treatment (baseline) refers to the IGF-1 level prior to the initiation of any somatostatin analog (e.g., Mycapssa® [octreotide delayed-release capsules], an octreotide acetate injection product [e.g., Bynfezia Pen™, Sandostatin® {generics}, Sandostatin® LAR Depot], Signifor® LAR [pasireotide for injectable

suspension], Somatuline® Depot [lanreotide subcutaneous injection]), dopamine agonist (e.g., cabergoline, bromocriptine), or Somavert® (pegvisomant for injection). Reference ranges for IGF-1 vary among laboratories.

L) The agent is prescribed by or in consultation with an endocrinologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Somavert is not recommended in the following situations:

254. Treatment of excess growth hormone associated with McCune-Albright syndrome (MAS). Five patients with growth hormone excess due to MAS were treated with 20 mg of Somavert daily for 12 weeks in a randomized double-blind placebo-controlled trial at the National Institutes of Health.[2] Somavert reduced IGF-1 and IGF binding protein-3 (IGFBP-3) in these patients but had no effect on fibrous dysplasia.

255. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

801. Somavert® for injection [prescribing information]. New York, New York: Pfizer; August 2019.
802. Akintoye SO, Kelly MH, Brillante B, et al. Pegvisomant for the treatment of gsp-mediated growth hormone excess in patients with McCune-Albright Syndrome. *J Clin Endocrinol Metab.* 2006;91:2960-2966.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/31/2019
Annual Revision	**Acromegaly.** In the Note section referring to the pre-treatment (baseline) insulin-like growth factor-1 (IGF-1) level, Mycapssa® (octreotide delayed-release capsules) and octreotide acetate injection products (Bynfezia Pen™, Sandostatin® [generics]) were added as examples of a somatostatin analog.	08/05/2020

PRIOR AUTHORIZATION POLICY

POLICY: Spinal Muscular Atrophy – Evrysdi Prior Authorization Policy

- Evrysdi® (risdiplam oral solution – Genentech/Roche)

REVIEW DATE: 08/12/2020; selected revision 09/30/2020 and 11/18/2020

OVERVIEW

Evrysdi, a survival motor neuron 2 (SMN2) splicing modifier, is indicated for the **treatment of spinal muscular atrophy** in patients 2 months of age and older.[1]

The recommended dosing is as follows:

- 0.2 mg/kg once daily (QD) for patients 2 months to < 2 years of age
- 0.25 mg/kg QD for patients ≥ 2 years of age and < 20 kg
- 5 mg for patients ≥ 2 years of age and ≥ 20 kg

Disease Overview

Spinal muscular atrophy is a genetic, autosomal recessive muscular disorder caused by deletion or loss of function mutation in the survival motor neuron 1 (SMN1) gene.[2-5] The reduced levels of survival motor neuron (SMN) protein causes degeneration of lower motor neurons.[5] Although the condition is a multisystem disorder, it is clinically

characterized by progressive muscle weakness and atrophy. Patients have difficulties with ambulation, head control, feeding and respiration. Cognitive development is not impacted. In the US, spinal muscular atrophy affects approximately one in 11,000 infants and has an average carrier frequency of one in 54 individuals; as many as 10,000 to 20,000 children and adults in the US may be impacted.[5] Although the condition can be present in individuals of any age, it is more frequently diagnosed in infants and children, as it is more severe in this population.[2-5] The phenotypic expression of the disease is impacted by the presence of the SMN2 gene copy number. SMN1 is responsible for producing most of the effective SMN protein, although some SMN protein can be made by the SMN2 gene. Therefore, patients with a deletion of the SMN1 gene may have the potential for making some SMN protein through the SMN2 gene copy, although in most cases the resulting protein made by this gene is truncated and is not as effective or functional. Data have shown that patients with a higher number of SMN2 copies generally have a more mild phenotypic disease expression. Gene deletion testing for spinal muscular atrophy can be performed at many diagnostic laboratories. Table 1 describes disease types. A different manner of categorization classifies the main three most common types as follows: Type 1 patients are "non-sitters", Type 2 patients are "sitters", and Type 3 patients are "walkers".[3,5]

Table 1. Types of Spinal Muscular Atrophy.[2-5]

SMA Type	Age at Onset	Features/Clinical Presentation	Lifespan	SMN2 Copy Gene Number
0	Prenatal	Severe hypotonia and weakness; respiratory failure at birth. There is no achievement of motor milestones.	A few weeks to < 6 months	0 to 1
1	< 6 months	Poor muscle tone, lack of movement, and respiratory assistance needed at birth. Patients are never able to sit.	< 2 years	1 to 2
2	Before 18 months	Patients are able to sit. However, patients are unable to walk or stand without assistance.	75% of patients are alive at 25 years of age	2 to 3
3	> 18 months	Walks independently but may lose this ability as the disease progresses.	Normal	3 to 4

Table 1 (continued). Types of Spinal Muscular Atrophy.[2-5]

SMA Type	Age at Onset	Features/Clinical Presentation	Lifespan	SMN2 Copy Gene Number
4	Adulthood	Walk until adulthood.	Normal lifespan	≥ 4

SMA – Spinal muscular atrophy; SMN2 – Survival motor neuron 2.

Besides Evrysdi, other therapies are available. **Spinraza®** (nusinersen injection for intrathecal use), a SMN2-directed antisense oligonucleotide, is indicated for the treatment of spinal muscular atrophy in pediatric and adult patients.[6] Spinraza is given by intrathecal injection. Although studies and experience continue, the primary pivotal data include infantile-onset (Type 1) and later-onset (Type 2 and Type 3) spinal muscular atrophy primarily in children. Trials are evolving with Spinraza in adults. Data are also available in presymptomatic infants who were genetically diagnosed with spinal muscular atrophy.

Zolgensma® (onasemnogene abeparvovec-xioi suspension for intravenous infusion), an adeno-associated virus vector-based gene therapy, is indicated for the treatment of pediatric patients < 2 years of age with spinal muscular atrophy with bi-allelic mutations in the SMN1 gene.[7] The agent works by providing a copy of the gene encoding the SMN protein, which increases its production. Zolgensma is administered as a single-dose intravenous infusion over 60 minutes. Pivotal studies mainly involve infants with two or three SMN2 gene copies with primarily Type 1 or Type 2 disease.

Clinical Efficacy

The efficacy of Evrysdi for the treatment of patients with infantile-onset (Type 1) and later-onset (Type 2 and 3) spinal muscular atrophy is being evaluated in two ongoing pivotal clinical trials.[1] **FIREFISH** is an open-label, two-part study designed to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of Evrysdi in patients with Type 1 spinal muscular atrophy who had symptom onset between 28 days and 3 months of age. Genetic confirmation of homozygous deletion or compound heterozygosity predictive or loss of function of the SMN1 gene was required for trial entry. Patients had two SMN2 gene copies. In Part 1 of the trial, the median age at enrollment was 6.7 months. For this population, of the patients who received the recommended dosage of Evrysdi (0.2 mg/kg QD) [n = 17], many patients gained improvements in the ability to sit for at least 5 seconds independently, as well as

in the percentages of patients who were alive without permanent ventilation. **SUNFISH** is a two-part, multicenter trial assessing the efficacy, safety, pharmacokinetics, and pharmacodynamics of Evrysdi in patients with later-onset (Type 2 or Type 3) spinal muscular atrophy. Most patients (90.2%) had three SMN2 gene copies; 7.8% and 2.0% of patients had four and two SMN2 gene copies, respectively. Part 2 of the study involved 180 nonambulatory patients who were randomized to receive Evrysdi at the FDA-approved dose or placebo. Benefits were noted at Month 12 in motor function as well as in upper limb motor performance. Of note, in general, the onset of effect with Evrysdi was observed after approximately 4 months of therapy.

Guidelines

Evrysdi is not addressed in guidelines. The Spinal Muscular Atrophy Newborn Screening Multidisciplinary Working Group is comprised of clinicians and geneticists with expertise in spinal muscular atrophy who developed a treatment algorithm in 2018 for infants who have positive results from a newborn screening test for spinal muscular atrophy.[8] Spinal muscular atrophy Types 1 and 2 comprise a large majority of cases and account for many patients who screen positively for spinal muscular atrophy with three or fewer SMN2 gene copies. Immediate treatment is recommended in patients with two or three SMN2 gene copies. Treatment recommendations for patients who screen positive for spinal muscular atrophy and have only one SMN2 gene copy is more complicated. It is likely that patients with only one SMN2 gene copy will likely be symptomatic at birth and the physician should determine if treatment is warranted.[8] In 2020, the Working Group updated recommendations that infants diagnosed with spinal muscular atrophy via newborn screening with four SMN2 gene copies should receive immediate treatment.[9] Also, patients with five (or more) SMN2 gene copies should observed and screened for symptoms.

Safety

Based on animal data, Evrysdi may cause fetal harm if given to a pregnant women.[1] Pregnancy testing is recommended for females of reproductive potential prior to initiating Evrysdi. Advise females of reproductive potential to use effective contraception during treatment with Evrysdi and for at least 1 month after the last dose. Because the efficacy and safety of Evrysdi in patients with hepatic impairment have not been studied, avoid use of this agent in patients with impaired hepatic function.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Evrysdi. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Evrysdi as well as the monitoring required for adverse events and long-term efficacy, approval requires Evrysdi to be prescribed by or in consultation with a physician who specializes in the condition being treated. For certain criteria, verification is required as noted by **[verification required by prescriber]**. All reviews will be forwarded to the Medical Director for evaluation.

Automation: None.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information. Subsequent coverage reviews for a patient who has previously met the documentation requirements and related criteria in the *Spinal Muscular Atrophy – Evrysdi Prior Authorization Policy* through the Coverage Review Department, and who is requesting reauthorization, the criteria utilized do NOT require re-submission of documentation for reauthorization, except for the criterion requiring documentation of response or benefit to Evrysdi therapy.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Evrysdi is recommended in those who meet the following criteria:

FDA-Approved Indications

261. Spinal Muscular Atrophy – Treatment. Approve if the patient meets ONE of the following criteria (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets all of the following criteria (i, ii, iii, iv, v, vi, vii, viii, and ix):

i. Patient is ≥ 2 months to ≤ 25 years of age; AND

ii. Patient has had a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene reported as at least one of the following: homozygous deletion, homozygous mutation, or compound heterozygous mutation **[documentation required]**; AND

iii. Patient meets both of the following (a and b):

a) Patient has two to four survival motor neuron 2 (SMN2) gene copies **[documentation required]**; AND

b) According to the prescriber, the patient has objective signs consistent with spinal muscular atrophy Types 1, 2, or 3 **[documentation required]**; AND

iv. For a patient currently receiving or who has received prior treatment with Spinraza® (nusinersen injection for intrathecal use), the prescriber attests that further therapy with Spinraza will be discontinued; AND

v. Patient has not received Zolgensma® (onasemnogene abeparvovec-xioi suspension for intravenous infusion) in the past **[verification required by prescriber]**; AND

Note: Verify through claims history that the patient has NOT previously received Zolgensma AND, if no claim for Zolgensma is present, the prescriber must attest that the patient has not previously received Zolgensma.

vi. Females of current reproductive potential must have the prescriber confirm BOTH of the following (a and b):

a) Patient is not currently pregnant; AND

b) Effective contraception will be utilized during treatment and for 1 month after the last Evrysdi dose; AND

vii. According to the prescriber, the patient does not have evidence of hepatic impairment; AND

viii. Dosing of Evrysdi meets ONE of the following based on the current (within the past 1 month) kg weight (a, b, or c):

a) 0.2 mg/kg once daily if the patient is 2 months to < 2 years of age; OR

b) 0.25 mg/kg once daily for patients ≥ 2 years of age who weigh < 20 kg; OR

c) 5 mg once daily for patients ≥ 2 years of age who weigh ≥ 20 kg; AND

ix. Medication is prescribed by a physician who has consulted with or who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders; OR

B) Patient is Currently Receiving Evrysdi. Approve for 4 months if the patient meets all of the following criteria (i, ii, iii, iv, v, vi, vii, viii, and ix):

i. Patient has had a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene reported as at least one of the following: homozygous deletion, homozygous mutation, or compound heterozygous mutation **[documentation required]**; AND

ii. Patient meets BOTH of the following (a and b):

a) Patient has two to four survival motor neuron 2 (SMN2) gene copies **[documentation required]**; AND

b) According to the prescriber, the patient has objective signs consistent with spinal muscular atrophy Types 1, 2, or 3 **[documentation required]**; AND

iii. For a patient currently receiving or who has received prior treatment with Spinraza® (nusinersen injection for intrathecal use), the prescriber attests that further therapy with Spinraza will be discontinued; AND

iv. Patient has NOT received Zolgensma® (onasemnogene abeparvovec-xioi suspension for intravenous infusion) in the past **[verification required by the prescriber]**; AND

Note: Verify through claims history that the patient has NOT previously received Zolgensma AND, if no claim for Zolgensma is present, the prescriber must attest that the patient has not previously received Zolgensma.

v. Females of current reproductive potential must have the prescriber confirm BOTH of the following (a and b):
- **a)** Patient is not currently pregnant; AND
- **b)** Effective contraception will be utilized during treatment and for 1 month after the last Evrysdi dose; AND

vi. According to the prescriber, the patient does not have evidence of hepatic impairment; AND

vii. Dosing of Evrysdi meets ONE of the following based on the current (within the past 1 month) kg weight (a, b, or c):
- **a)** 0.2 mg/kg if the patient is 2 months to < 2 years of age; OR
- **b)** 0.25 mg/kg for patients ≥ 2 years of age who weigh < 20 kg; OR
- **c)** 5 mg for patients ≥ 2 years of age who weigh ≥ 20 kg; AND

viii. Medication is prescribed by a physician who has consulted with or who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders; AND

ix. According to the prescriber, the patient has responded to Evrysdi or continues to have benefit from ongoing Evrysdi therapy by the most recent (within the past 4 months) objective measurement and/or assessment tool **[documentation required]**.

Note: Examples of improvement, achievement, and/or maintenance in motor milestones should be demonstrated and can be evaluated by tests such as the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) [Item 22], Motor Function Measure-32 Items (MFM-32), Hammersmith Infant Neurologic Exam (HINE) [section 2], Hammersmith Functional Motor Scale Expanded (HFMSE), Children's Hospital of Philadelphia Test of Neuromuscular Disorders (CHOP-INTEND), as well as other physician monitoring tools (pulmonary function tests showing improvement, bulbar function results, reduced need for respiratory support, and/or prevention of permanent assisted ventilation).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Evrysdi is not recommended in the following situations:

256. Patient has Complete Paralysis of All Limbs. Data are needed to determine if this patient population with advanced spinal muscular atrophy would derive benefits from Evrysdi.

257. Patient has Permanent Ventilator Dependence. Data are needed to determine if this patient population with advanced spinal muscular atrophy would derive benefits from Evrysdi.

258. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	08/12/2020
Selected Revision	**Spinal Muscular Atrophy – Treatment:** For a patient using Evrysdi for spinal muscular atrophy (treatment) who are currently receiving Evrysdi, the requirement that the patient is ≥ 2 months of age and ≤ 25 years of age was removed. Also, regarding the criteria pertaining to Spinraza, wording was added to include not only those who have received prior treatment with Spinraza, but also those "currently receiving" the therapy; it should be attested that the therapy will not be further given with Spinraza use. A slight change was made to the documentation statement. For this related criterion regarding patients currently receiving Evrysdi therapy, it was specified that "the most recent (within the last 4 months)" objective measurement and/or assessment tool will be utilized. **Documentation:** Wording was added that for subsequent coverage reviews for a patient who has previously met the documentation requirements and related criteria in the *Spinal Muscular Atrophy – Evrysdi Prior Authorization Policy* through the Coverage Review Department, and who is requesting reauthorization, the criteria utilized do NOT require re-submission of documentation for reauthorization, except for the criterion requiring documentation of response or benefit to Evrysdi therapy.	09/30/2020
Selected Revision	**Spinal Muscular Atrophy – Treatment:** The criteria that requires the medication to be prescribed by or in consultation with a with a physician who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders was changed to "medication is prescribed by a physician who has consulted with or who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders".	11/18/2020

PRIOR AUTHORIZATION POLICY

POLICY: Spinal Muscular Atrophy – Spinraza Prior Authorization Policy
- Spinraza® (nusinersen injection for intrathecal use – Biogen)

REVIEW DATE: 6/03/2020; selected revision 08/12/2020, 09/09/2020 and 11/18/2020

OVERVIEW

Spinraza, a survival motor neuron 2 (SMN2)-directed antisense oligonucleotide, is indicated for the treatment of spinal muscular atrophy in pediatric and adult patients.[1]

Disease Overview

Spinal muscular atrophy is a genetic, autosomal recessive muscular disorder caused by deletion or loss of function mutation in the survival motor neuron 1 (SMN1) gene.[2-5] The reduced levels of survival motor neuron (SMN) protein causes degeneration of lower motor neurons.[5] Although the condition is a multisystem disorder, it is clinically characterized by progressive muscle weakness and atrophy. Patients have difficulties with ambulation, head control, feeding, and respiration. Cognitive development is not impacted. In the US, spinal muscular atrophy affects approximately one in 11,000 infants and has an average carrier frequency of one in 54 individuals; as many as 10,000 to 20,000 children and adults in the US may be impacted.[5] Although the condition can be present in individuals of any age, it is more frequently diagnosed in infants and children, as it is more severe in this population.[2-5] The phenotypic expression of

the disease is impacted by the presence of the SMN2 gene copy number. SMN1 is responsible for producing most of the effective SMN protein, although some SMN protein can be made by the SMN2 gene. Therefore, patients with a deletion of the SMN1 gene may have the potential for making some SMN protein through the SMN2 gene copy, although in most cases the resulting protein made by this gene is truncated and is not as effective or functional. Data have shown that patients with a higher number of SMN2 copies generally have a more mild phenotypic disease expression. Gene deletion testing for spinal muscular atrophy can be performed at many diagnostic laboratories. Table 1 describes disease types. A different manner of categorization classifies the three most common types as follows: Type 1 patients are "non-sitters", Type 2 patients are "sitters", and Type 3 patients are "walkers".[3,5]

Table 1. Types of Spinal Muscular Atrophy.[2-5]

SMA Type	Age at Onset	Features/Clinical Presentation	Lifespan	SMN2 Copy Gene Number
0	Prenatal	Severe hypotonia and weakness; respiratory failure at birth. There is no achievement of motor milestones.	A few weeks to < 6 months	0 to 1
1	< 6 months	Poor muscle tone, lack of movement, and respiratory assistance needed at birth. Patients are never able to sit.	< 2 years	1 to 2
2	Before 18 months	Patients are able to sit. However, patients are unable to walk or stand without assistance.	75% of patients are alive at 25 years of age	2 to 3
3	> 18 months	Walks independently but may lose this ability as the disease progresses.	Normal	3 to 4
4	Adulthood	Walk until adulthood.	Normal lifespan	≥ 4

SMA – Spinal muscular atrophy; SMN2 – Survival motor neuron 2.

Besides Spinraza, other therapies are available. **Evrysdi®** (risdiplam oral solution), a SMN2 splicing modifier, is indicated for the treatment of spinal muscular atrophy in patients 2 months of age and older.[6] The primary pivotal data include infantile-onset (Type 1) and later-onset (Type 2 and Type 3) spinal muscular atrophy primarily in children and adults up to 25 years of age. Trials are ongoing in older adults, as well as in presymptomatic infants who were genetically diagnosed with spinal muscular atrophy.

Zolgensma® (onasemnogene abeparvovec-xioi suspension for intravenous infusion), an adeno-associated virus vector-based gene therapy, is indicated for the treatment of pediatric patients < 2 years of age with spinal muscular atrophy with bi-allelic mutations in the SMN1 gene.[7] The agent works by providing a copy of the gene encoding the SMN protein, which increases its production. Zolgensma is administered as a single-dose intravenous infusion over 60 minutes. Pivotal studies mainly involve infants with two or three SMN2 gene copies with primarily Type 1 or Type 2 disease.

Clinical Efficacy

Spinraza was investigated in a pivotal trial called ENDEAR, which was a Phase III, multicenter, multinational, randomized, double-blind, sham-procedure controlled study involving 121 symptomatic infants diagnosed with infantile-onset spinal muscular atrophy (Type I).[1,8] Patients were randomized 2:1 to receive either Spinraza (n = 80) or sham injection (n = 41).[1] Eligible patients were ≤ 7 months of age at the time of the first dose and diagnosed with spinal muscular atrophy with a symptom onset prior to 6 months of age. A planned interim efficacy analysis was performed based on patients who died, withdrew, or completed at least 183 days of treatment. Baseline demographics were balanced between the Spinraza and control groups with the exception of age at first treatment (median age of 175 and 206 days, respectively).[1] At baseline, all infants were symptomatic, hypotonic and weak, which are features consistent with a phenotype that is most likely to be categorized as spinal muscular atrophy Type 1.[8] Patients had two SMN2 gene copies. The median time of treatment was 261 days (range 6 to 442 days).[1] Those who received Spinraza compared with sham-control experienced improvement on achieving motor

milestone responses. Outcomes assessing survival also revealed improvements for patients receiving Spinraza vs. sham control.

CHERISH was a multicenter, double-blind, sham-controlled, Phase III trial which involved children with symptomatic later-onset spinal muscular atrophy who were 2 to 12 years of age (n = 126) with likely Type 2 or 3 disease (symptom onset after 6 months of age).[1,9] Patients were randomized (2:1) to receive Spinraza or sham injection. Patients had genetically-confirmed 5q spinal muscular atrophy.[9] Three SMN2 gene copies were reported among 88% of patients; approximately 8% of patients had two SMN2 gene copies. The median age at screening was 4 years and 3 years in the Spinraza and sham procedure control groups, respectively.[1,9] Patients who received Spinraza experienced more improvement in motor milestones compared with sham control.

NURTURE was an open-label uncontrolled trial involving patients with presymptomatic spinal muscular atrophy who ranged in age from 3 days to 42 days at the time of the first dose (n = 25).[1,10] For study inclusion, patients were required to have two or three SMN2 gene copies.[10] Some patients who were given Spinraza prior to the onset of symptoms related to spinal muscular atrophy survived without requiring permanent ventilation beyond what would be anticipated based on their SMN2 copy number. Also, some patients also met age-appropriate growth and development motor milestones (e.g., ability to sit unassisted, stand, or walk). Data are available from almost a median of 3-year follow-up.

Other data with Spinraza are also available and data are accumulating in adults.[11-18] Follow-up is available for up to 4 years. Patients experienced a reversal of decline, achieved milestones, and experienced additional improvement in scales assessing motor function.

Dosing

Spinraza is given intrathecally by, or under the direction of, healthcare professionals experienced in performing lumbar punctures.[1] The recommended dosage is 12 mg (5 mL) per administration. Initiate Spinraza treatment with four loading doses. The first three loading doses should be administered at 14-day intervals. The fourth loading dose should be given 30 days after the third dose. A maintenance dose should be given once every 4 months thereafter. The safety and effectiveness of Spinraza in pediatric patients from newborn to 17 years of age have been established.

Guidelines

The Spinal Muscular Atrophy Newborn Screening Multidisciplinary Working Group is comprised of clinicians and geneticists with expertise in spinal muscular atrophy who developed a treatment algorithm in 2018 for infants who have positive results from a newborn screening test for spinal muscular atrophy.[19] Spinal muscular atrophy Types 1 and 2 comprise a large majority of cases and account for many patients who screen positively for spinal muscular atrophy with three or fewer SMN2 gene copies. Immediate treatment is recommended in patients with two or three SMN2 gene copies. Treatment recommendations for patients who screen positive for spinal muscular atrophy and have only one SMN2 gene copy is more complicated. It is likely that patients with only one SMN2 gene copy will likely be symptomatic at birth and the physician should determine if treatment is warranted.[19] In 2020, the Working Group updated recommendations that infants diagnosed with spinal muscular atrophy via newborn screening with four SMN2 gene copies should receive immediate treatment.[20] Also, patients with five (or more) SMN2 gene copies should be observed and screened for symptoms.

Safety

Spinraza has Warnings/Precautions regarding thrombocytopenia and coagulation abnormalities, as well as renal toxicity. Due to the increased risk of bleeding complications and renal toxicity, testing is required at baseline and prior to each dose. The following laboratory tests should be performed at baseline and prior to each Spinraza dose, and as clinically needed: platelet count; prothrombin time; activated partial thromboplastin time; and quantitative spot urine protein testing.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Spinraza. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Due to the specialized skills required for evaluation and diagnosis of patients treated with Spinraza, as well as the monitoring required for adverse events and long-term efficacy, approval requires Spinraza to be prescribed by or in consultation with a physician who specializes in the condition being treated. All reviews will be forwarded to the Medical Director for evaluation.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information. Subsequent coverage reviews for a patient who has previously met the documentation requirements and related criteria in the *Spinal Muscular Atrophy – Spinraza Prior Authorization Policy* through the Coverage Review Department, and who is requesting reauthorization, the criteria utilized do NOT require re-submission of documentation for reauthorization, except for the criterion requiring documentation of response or benefit to Spinraza therapy. For certain criteria, verification is required as noted by **[verification required by prescriber]**. All reviews will be forwarded to the Medical Director for evaluation.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Spinraza is recommended in those who meet the following criteria:

FDA-Approved Indication

~~94.~~91. **Spinal Muscular Atrophy** – **Treatment.** Approve for the duration noted if the patient meets ONE of the following (A or B):

D) Initial Therapy. Approve for 3 months if the patient meets all of the following criteria (i, ii, iii, iv, v, and vi):

i. Patient has had a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene reported as at least one of the following: homozygous deletion, homozygous mutation, or compound heterozygous mutation **[documentation required]**; AND

ii. Patient meets one of the following (a or b):

a) Patient has two or three survival motor neuron 2 (SMN2) gene copies **[documentation required]**; OR

b) Patient meets both of the following criteria [(1) and (2)]:

(1) The patient has four survival motor neuron 2 (SMN2) gene copies **[documentation required]**; AND

(2) According to the prescriber, the patient has objective signs consistent with spinal muscular atrophy Types 1, 2, or 3 **[documentation required]**; AND

iii. For a patient currently receiving or who has received prior treatment with Evrysdi® (risdiplam oral solution), the prescriber attests that further therapy with Evrysdi will be discontinued; AND

iv. Patient has not received Zolgensma® (onasemnogene abeparvovec-xioi suspension for intravenous infusion) in the past **[verification required by prescriber]**; AND

Note: Verify through claims history that the patient has not previously received Zolgensma AND, if no claim for Zolgensma is present, the prescriber must attest that the patient has not previously received Zolgensma.

v. The following laboratory tests will be evaluated prior to the administration of Spinraza (a, b, and c):

a) Prothrombin time and/or activated partial thromboplastin time; AND

b) Platelet count; AND

c) Quantitative spot urine protein testing; AND

vi. Medication is prescribed by a physician who has consulted with or who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders; OR

E) Patients Currently Receiving Spinraza Therapy. Approve one dose (for a dose to be used once within the next 4 months as maintenance therapy) if the patient meets all of the following criteria (i, ii, iii, iv, v, vi, and vii):

i. Patient has had a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene reported as at least one of the following: homozygous deletion, homozygous mutation, or compound heterozygous mutation **[documentation required]**; AND

ii. Patient meets one of the following (a or b):

a) Patient has two or three survival motor neuron 2 (SMN2) gene copies **[documentation required]**; OR

b) Patient meets both of the following [(1) and (2)]:

(1) Patient has four survival motor neuron 2 (SMN2) gene copies **[documentation required]**; AND

(2) According to the prescriber the patient has objective signs consistent with spinal muscular atrophy Types 1, 2, or 3 **[documentation required]**; AND

iii. For a patient currently receiving or who has received prior treatment with Evrysdi® (risdiplam oral solution), the prescriber attests that further therapy with Evrysdi will be discontinued; AND

iv. Patient has not received Zolgensma® (onasemnogene abeparvovec-xioi suspension for intravenous infusion) in the past **[verification required by prescriber]**; AND
Note: Verify through claims history that the patient has not previously received Zolgensma AND, if no claim for Zolgensma is present, the prescriber must attest that the patient has not previously received Zolgensma.

v. The following laboratory tests will be evaluated prior to administration of Spinraza (a, b, and c):
- **a)** Prothrombin time and/or activated partial thromboplastin time; AND
- **b)** Platelet count; AND
- **c)** Quantitative spot urine protein testing; AND

vi. Medication is prescribed a physician who has consulted with or who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders; AND

vii. According to the prescriber, the patient has responded to Spinraza or continues to have benefit from ongoing Spinraza therapy by the most recent (i.e., within the past 3 months) objective measurement and/or assessment tool **[documentation required]**.
Note: Examples of improvement, achievement, and/or maintenance in motor milestones should be demonstrated and can be evaluated by tests such as the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) [Item 22], Motor Function Measure-32 Items (MSM-32), Hammersmith Infant Neurologic Exam (HINE) [section 2], Hammersmith Functional Motor Scale Expanded (HFMSE), Children's Hospital of Philadelphia Test of Neuromuscular Disorders (CHOP-INTEND) as well as other physician monitoring tools (pulmonary function tests showing improvement, bulbar function tests, reduced need for respiratory support, and/or prevention of permanent assisted ventilation).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Spinraza is not recommended in the following situations:

259. Patient has Complete Paralysis of All Limbs. Data are needed to determine if this patient population with advanced spinal muscular atrophy would derive benefits from Spinraza.

260. Patient has Permanent Ventilator Dependence. Data are needed to determine if this patient population with advanced spinal muscular atrophy would derive benefits from Spinraza.

261. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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61. Glascock J, Sampson J, Connolly AM, et al. Revised recommendations for the treatment of infants diagnosed with spinal muscular atrophy via newborn screening who have 4 copies of SMN2. *J Neuromuscul Dis*. 2020;7(2):97-100.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Update	5/24/2019: No criteria changes. The title Spinal Muscular Atrophy was added to the name of the policy.	--
Annual revision	All Spinraza reviews will be done by the Medical Director. Changes below in criteria are described below. **Spinal Muscular Atrophy, Treatment:** The same criteria changes were made for patients who were receiving initial therapy and in patients currently receiving Spinraza Therapy. The notation of Type I, II, or III spinal muscular atrophy was removed. The criteria regarding the genetic test had the term "bi-allelic mutations" added. Criteria were added that the patient has two or three survival motor neuron 2 (SMN2) gene copies (with documentation required) or that the patient has four or more SMN2 gene copies (with documentation required) AND according to the prescribing physician the patient has symptoms consistent with Types 1, 2, or 3 spinal muscular atrophy. Criteria were added that the patient has not received Zolgensma® (onasemnogene abeparvovec-xioi suspension for intravenous infusion) in the past. It was added that the following laboratory tests will be evaluated prior to the administration of Spinraza: a) Prothrombin time and/or activated partial thromboplastin time; b) Platelet count; and c) Quantitative spot urine protein testing. **Conditions Not Recommended for Approval:** A criterion was added to not approve Spinraza if the patient has complete paralysis of limbs to suggest advanced spinal muscular atrophy. Additionally, a criterion was added to not approve Spinraza if the patient has permanent ventilator dependence to suggest advanced spinal muscular atrophy. In these clinical scenarios, data are needed to determine if this patient population would derive benefits from Spinraza.	06/18/2019
Selected revision	"Prescriber" replaced the phrase "prescribing physician" in applicable places in the criteria. For patients currently receiving Spinraza therapy that was approved through a request from the ESI coverage review department, a note was added stating to provide an exception to the requirement of SMN2 gene copy information if, according to the prescriber, the patient has symptoms consistent with spinal muscular atrophy Types 1, 2 or 3.	01/15/2020
Selected revision	Approval for initial therapy was changed from 12 months to 3 months. Approval for patients currently receiving Spinraza therapy was changed from 12 months to one dose (for a dose to be used once within the next 4 months for maintenance therapy). For the criteria that requires that the patient has not received Zolgensma in the past, a note was added to verify through claims history that the patient has not previously received Zolgensma AND, if no claim for Zolgensma is present, the prescriber must attest that the patient has not previously received Zolgensma. For the requirement for patients who are currently receiving therapy that the patient has responded to Spinraza, a documentation requirement was added. Also, examples of response to therapy was moved from the criteria to a note.	03/25/2020
Annual revision	No criteria changes.	06/03/2020

HISTORY (CONTINUED)

Type of Revision	Summary of Changes	Date Reviewed
Selected revision	**Spinal Muscular Atrophy – Treatment:** Criteria regarding survival motor neuron 2 (SMN2) gene copies for patients receiving initial therapy and for those currently receiving Spinraza therapy were altered such that the patient must have between two to four SMN2 gene copies and have objective signs consistent with spinal muscular atrophy Type 1, 2 or 3; documentation is required for these criteria. Previously, a patient with two or three SMN2 gene copies was approved (with documentation required) whereas a patient with four or more SMN2 gene copies had to also have symptoms consistent with spinal muscular atrophy Types 1, 2 or 3. A requirement was added that for a patient who has received prior treatment with Evrysdi (risdiplam oral solution), the prescriber attests that further therapy with Evrysdi will be discontinued. It was emphasized that verification is required by the prescriber that the patient has not received Zolgensma in the past. For a patient who has been previously receiving Spinraza, wording of the criteria were altered from "the patient has responded to Spinraza therapy" to "the patient has responded to Spinraza or continues to have benefit from ongoing Spinraza therapy by an objective measurement and/or assessment tool". Also, additional scales and tests were added to the Note that provides examples of improvement achievement and/or maintenance in motor milestones. **Conditions Not Recommended for Approval:** The condition regarding paralysis of limbs was simplified from "The patient has complete paralysis of limbs to suggest advanced spinal muscular atrophy" to "Patient has Complete Paralysis of All Limbs". The condition regarding permanent ventilator dependence was simplified from "The patient has permanent ventilator dependence to suggest advanced spinal muscular atrophy" to "Patient has Permanent Ventilator Dependence."	08/12/2020
Selected revision	A change was made to the criteria regarding the diagnosis of Spinal Muscular Atrophy – Treatment. Patients with two or three SMN2 gene copies are no longer required to have objective signs consistent with spinal muscular atrophy; patients with four SMN2 gene copies still must meet this criterion. Also, regarding the criteria pertaining to Evrysdi, wording was added to include not only those who have received prior treatment with Evrysdi, but also those "currently receiving" the therapy; it should be attested that the therapy will not be further given with Spinraza use. A slight change was made to the documentation statement. Wording was added that for subsequent coverage reviews for a patient who has previously met the documentation requirements and related criteria in the *Spinal Muscular Atrophy – Spinraza Prior Authorization Policy* through the Coverage Review Department, and who is requesting reauthorization, the criteria utilized do NOT require re-submission of documentation for reauthorization, "except for the criterion requiring documentation of response or benefit to Spinraza therapy." For this related criterion regarding patients currently receiving Spinraza therapy, it was specified that "the most recent (within the last 3 months)" objective measurement and/or assessment tool will be utilized.	09/09/2020
Selected Revision	**Spinal Muscular Atrophy – Treatment:** The criteria that requires the medication to be prescribed by or in consultation with a physician who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders was changed to "medication is prescribed by a physician who has consulted with or who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders". In patients currently receiving therapy, the Note was removed that stated that "if the patient is currently receiving Spinraza that was approved through a request from the coverage review department, an exception to the requirement of SMN2 gene copy information may be granted if, according to the prescriber, the patient has objective signs consistent with spinal muscular atrophy Types 1, 2, or 3."	11/18/2020

SMN2 – Survival motor neuron 2.

PRIOR AUTHORIZATION POLICY

POLICY: Spinal Muscular Atrophy – Zolgensma Prior Authorization Policy

- Zolgensma® (onasemnogene abeparvovec-xioi suspension for intravenous infusion – AveXis)

OVERVIEW

Zolgensma, an adeno-associated virus vector-based gene therapy, is indicated for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene.[1]

Limitations of use are that the safety and effectiveness of repeat administration of Zolgensma have not been evaluated.[1] The use of Zolgensma in patients with advanced spinal muscular atrophy (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been assessed. Use of Zolgensma in premature neonates before reaching full-term gestational age is not recommended because concomitant treatment with corticosteroids may adversely affect neurological development. Zolgensma therapy should be delayed until full-term gestational age is achieved.[1] The definition of full-term pregnancy commences at 39 weeks and 0 days gestation.[2]

Disease Overview

Spinal muscular atrophy is a genetic, autosomal recessive muscular disorder caused by deletion or loss of function mutation in the SMN1 gene.[3-6] The reduced levels of survival motor neuron (SMN) protein causes degeneration of lower motor neurons.[6] Although the condition is a multisystem disorder, it is clinically characterized by progressive muscle weakness and atrophy. Patients have difficulties with ambulation, head control, feeding and respiration. Cognitive development is not impacted. In the US, spinal muscular atrophy affects approximately one in 11,000 infants and has an average carrier frequency of one in 54 individuals; as many as 10,000 to 20,000 children and adults in the US may be impacted.[6] Although the condition can be present in individuals of any age, it is more frequently diagnosed in infants and children, as it is more severe in this population.[3-6] The phenotypic expression of the disease is impacted by the presence of the SMN2 gene copy number. SMN1 is responsible for producing most of the effective SMN protein, although some SMN protein can be made by the SMN2 gene. Therefore, patients with a deletion of the SMN1 gene may have the potential for making some SMN protein through the survival motor neuron 2 (SMN2) gene copy, although in most cases the resulting protein made by this gene is truncated and is not as effective or functional. Data have shown that patients with a higher number of SMN2 gene copies generally have a more mild phenotypic disease expression. Gene deletion testing for spinal muscular atrophy can be performed at many diagnostic laboratories. Table 1 describes disease types. A different manner of categorization classifies the main three most common types as follows: Type 1 patients are "non-sitters", Type 2 patients are "sitters", and Type 3 patients are "walkers".[4,6]

Table 1. Types of Spinal Muscular Atrophy.[3-6]

SMA Type	Age at Onset	Features/Clinical Presentation	Lifespan	SMN2 Gene Copy Number
0	Prenatal	Severe hypotonia and weakness; respiratory failure at birth. There is no achievement of motor milestones.	A few weeks to < 6 months	0 to 1
1	< 6 months	Poor muscle tone, lack of movement, and respiratory assistance needed at birth. Patients are never able to sit.	< 2 years	1 to 2

Table 1 (continued). Types of Spinal Muscular Atrophy.[2-5]

SMA Type	Age at Onset	Features/Clinical Presentation	Lifespan	SMN2 Gene Copy Number
2	Before 18 months	Patients are able to sit. However, patients are unable to walk or stand without assistance.	75% of patients are alive at 25 years of age	2 to 3
3	> 18 months	Walks independently but may lose this ability as the disease progresses.	Normal	3 to 4
4	Adulthood	Walk until adulthood.	Normal lifespan	≥ 4

SMA – Spinal muscular atrophy; SMN2 – Survival motor neuron 2.

Besides Zolgensma, other therapies are available. **Spinraza®** (nusinersen injection for intrathecal use), a SMN2-directed antisense oligonucleotide, is indicated for the treatment of spinal muscular atrophy in pediatric and adult

patients.[7] Spinraza is given by intrathecal injection. Although studies and experience continue, the primary pivotal data include infantile-onset (Type 1) and later-onset (Type 2 and Type 3) spinal muscular atrophy primarily in children. Trials are evolving with Spinraza in adults. Data are also available in presymptomatic infants who were genetically diagnosed with spinal muscular atrophy.

Evrysdi® (risdiplam oral solution), a SMN2 splicing modifier, is indicated for the treatment of spinal muscular atrophy in patients 2 months of age and older.[8] The primary pivotal data include infantile-onset (Type 1) and later-onset (Type 2 and Type 3) spinal muscular atrophy primarily in children and adults up to 25 years of age. Trials are ongoing in older adults, as well as in presymptomatic infants who were genetically diagnosed with spinal muscular atrophy.

Clinical Efficacy

The efficacy of Zolgensma was established in patients less than 2 years of age with spinal muscular atrophy who had bi-allelic mutations in the SMN1 gene.[1,9] One trial was an open-label, single-arm study which is ongoing and the other was an open-label, single-arm, ascending-dose clinical trial.[1] Symptoms onset occurred before patients were 6 months of age. All patients had genetically confirmed bi-allelic SMN1 gene deletions and two SMN2 gene copies. In both trials, Zolgensma was given as a single-dose intravenous infusion. Efficacy was assessed on parameters such as survival and achievement of developmental motor milestones (e.g., sitting without support). The definition of survival was at the time from birth to either death or permanent ventilation. Other efficacy parameters were evaluated (e.g., assessment of Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders [CHOP-INTEND] scores, evaluation of ventilator use). The ongoing clinical trial involved 21 patients with infantile-onset spinal muscular atrophy. The mean CHOP-INTEND score was 31.0 (range, 18 to 47). The mean patient age at the time of treatment was 3.9 months (range, 0.5 to 5.9 months). As of the March 2019 cutoff date, 19 patients were alive without permanent ventilation. Compared with natural history data Zolgensma is effective as more patients attained the ability to sit without support.[1] The completed clinical trial involved 15 patients with infantile-onset spinal muscular atrophy.[1,9] Three patients were in a low-dose cohort and 12 patients were in a high-dose cohort.[1] At the time of treatment, the mean age of patients in the low-dose cohort was 6.3 months (range, 5.9 to 7.2 months) and 3.4 months (range, 0.9 to 7.9 months) in the high-dose group. The dose in the low-dose cohort was approximately one-third of the dosage received by patients in the high-dose cohort. At 24 months following Zolgensma infusion, one patient in the low-dose cohort met the endpoint of permanent ventilation; all 12 patients in the high-dose cohort were alive without permanent ventilation. In the high-dose cohort, 9 of 12 patients (75%) were able to stand and walk without assistance.[1,9] Additional data supports benefits in patients in the high-dose cohort.[10-12]

Guidelines

The Spinal Muscular Atrophy Newborn Screening Multidisciplinary Working Group is comprised of clinicians and geneticists with expertise in spinal muscular atrophy who developed a treatment algorithm in 2018 for infants who have positive results from a newborn screening test for spinal muscular atrophy.[13] Spinal muscular atrophy Types 1 and 2 comprise a large majority of cases and account for many patients who screen positively for spinal muscular atrophy with three or fewer SMN2 gene copies. Immediate treatment is recommended in patients with two or three SMN2 gene copies. Treatment recommendations for patients who screen positive for spinal muscular atrophy and have only one SMN2 gene copy is more complicated. It is likely that patients with only one SMN2 gene copy will likely be symptomatic at birth and the physician should determine if treatment is warranted.[13] In 2020, the Working Group updated recommendations that infants diagnosed with spinal muscular atrophy via newborn screening with four SMN2 gene copies should receive immediate treatment.[14] Also, patients with five (or more) SMN2 gene copies should be observed and screened for symptoms.

Dosing

The recommended dose of Zolgensma is 1.1 x 10^{14} vector genomes (vg) per kg of body weight.[1] Administer Zolgensma as an intravenous infusion over 60 minutes. Starting 1 day prior to Zolgensma infusion, give systemic corticosteroids equivalent to oral prednisolone 1 mg/kg of body weight for a total of 30 days. Examine liver function after this juncture and follow recommended guidelines.

Safety

Zolgensma has a Boxed Warning regarding acute serious liver injury.[1] Elevated aminotransferases can occur with Zolgensma. Patients with preexisting liver impairment may be at higher risk. Prior to infusion, evaluate liver function in all patients by clinical examination and laboratory testing. One day before Zolgensma infusion, commence administration of systemic corticosteroids equivalent to oral prednisolone at 1 mg per kg of body weight per day for a total of 30 days. Transient decreases in platelet counts may occur. Therefore, measure platelet counts prior to the infusion, weekly for the first month, and then once every other week for the second and third month until platelet counts return to baseline. Also, temporary increases in cardiac troponin-I levels were noted with Zolgensma administration. Therefore, assess troponin-I prior to the infusion, as well as weekly for the first month and then monthly for the second and third until troponin-I level returns to baseline. Perform baseline anti-AAV9 antibody testing prior to Zolgensma infusion. Patients in the Zolgensma trials were required to have baseline anti-AAV9 antibody titers of ≤ 1:50.

POLICY STATEMENT

Prior authorization is recommended for benefit coverage of Zolgensma. Approval is recommended for those who meet the Criteria for the listed indication(s). Because of the of the specialized skills required for evaluation and diagnosis of patients treated with Zolgensma as well as the specialized training required for administration of Zolgensma, approval requires Zolgensma to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for one dose per lifetime. All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation. For certain criteria, verification is required as noted by **[verification required by prescriber]**.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to chart notes and/or laboratory data.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zolgensma is recommended in those who meet the following criteria:

FDA-Approved Indication

35. **Spinal Muscular Atrophy – Treatment.** Approve for a one-time per lifetime dose if the patient meets the following criteria (A, B, C, D, E, F, G, H, I, J, K, and L):
    A) Patient is less than 2 years of age; AND

B) If the patient is a premature neonate, full-term gestational age of 39 weeks and 0 days has been met; AND

C) Patient has had a genetic test confirming the diagnosis of spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene reported as at least one of the following: homozygous deletion, homozygous mutation, or compound heterozygous mutation **[documentation required]**; AND

D) Patient has three or fewer survival motor neuron 2 (SMN2) gene copies **[documentation required]**; AND

E) Patient has started or will receive systemic corticosteroids equivalent to oral prednisolone at a dose of 1 mg/kg per day commencing 1 day prior to Zolgensma infusion and for a total of 30 days; AND

F) Baseline anti-AAV9 antibody titers are ≤ 1:50; AND

G) The following laboratory tests will be evaluated prior to administration of Zolgensma (i, ii, and iii):

- **i.** Baseline liver function testing (e.g., aspartate aminotransferase, alanine aminotransferase, total bilirubin, prothrombin time); AND
- **ii.** Platelet count; AND
- **iii.** Troponin-I levels; AND

H) The patient has not received Zolgensma in the past **[verification required by prescriber]**; AND
Note: Verify through claims history that the patient has not previously received Zolgensma AND, if no claim for Zolgensma is present, the prescriber must attest that the patient has not previously received Zolgensma.

I) For a patient currently receiving or who has received prior treatment with Spinraza® (nusinersen injection for intrathecal use), the prescriber attests that further therapy with Spinraza will be discontinued; AND

J) For a patient currently receiving or who has received prior treatment with Evrysdi® (risdiplam oral solution), the prescriber attests that further therapy with Evrysdi will be discontinued; AND

K) Medication is prescribed by a physician who has consulted with or who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders; AND

L) If criteria A through K are met, approve one dose (kit) of Zolgensma based on the current weight in kg (within the past 14 days) **[documentation required]** per the cited NDC as in Table 2 below.

Table 2. Dose of Zolgensma Based on Availability.[1]

Patient Weight Range (kg)	Dose Volume (mL)*	Zolgensma Kit Configuration			NDC Number
		5.5 mL vial	8.3 mL vial	Total Vials per Kit	
2.6 to 3.0	16.5	0	2	2	71894-120-02
3.1 to 3.5	19.3	2	1	3	71894-121-03
3.6 to 4.0	22.0	1	2	3	71894-122-03
4.1 to 4.5	24.8	0	3	3	71894-123-03
4.6 to 5.0	27.5	2	2	4	71894-124-04
5.1. to 5.5	30.3	1	3	4	71894-125-04
5.6 to 6.0	33.0	0	4	4	71894-126-04
6.1 to 6.5	35.8	2	3	5	71894-127-05
6.6 to 7.0	38.5	1	4	5	71894-128-05
7.1 to 7.5	41.3	0	5	5	71894-129-05
7.6 to 8.0	44.0	2	4	6	71894-130-06
8.1 to 8.5	46.8	1	5	6	71894-131-06
8.6 to 9.0	49.5	0	6	6	71894-132-06
9.1 to 9.5	52.3	2	5	7	71894-133-07
9.6 to 10.0	55.0	1	6	7	71894-134-07
10.1 to 10.5	57.8	0	7	7	71894-135-07
10.6 to 11.0	60.5	2	6	8	71894-136-08
11.1 to 11.5	63.3	1	7	8	71894-137-08
11.6 to 12.0	66.0	0	8	8	71894-138-08
12.1 to 12.5	68.8	2	7	9	71894-139-09
12.6 to 13.0	71.5	1	8	9	71894-140-09
13.1 to 13.5	74.3	0	9	9	71894-141-09
≥ 13.6 kg†	Refer to the medical director for approval of specific NDCs				

* Dose volume is calculated using the upper limit of the patient weight range for pediatric patients less than 2 years of age between 2.6 kg and 13.5 kg; † Dose volume for pediatric patients less than 2 years of age weighing equal to or greater than 13.6 kg will require a combination of Zolgensma kits.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zolgensma is not recommended in the following situations:

262. Patient has Four or More Survival Motor Neuron 2 (SMN2) Gene Copies. These patients were not studied and guidance does not recommend treatment.

263. Patient has Complete Paralysis of All Limbs. This is cited as a limitation of use in the Zolgensma prescribing information.[1] Data are needed to determine if this patient population would derive benefits from Zolgensma.

264. Patient has Permanent Ventilator Dependence. This is cited as a limitation of use in the Zolgensma prescribing information.[1] Data are needed to determine if this patient population would derive benefits from Zolgensma.

265. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	Not applicable	05/24/2019
Selected Revision	**Spinal Muscular Atrophy, Treatment:** A documentation requirement was added in the criterion that requires that the patient has three or fewer survival motor neuron 2 (SMN2) gene copies. Regarding the laboratory tests criteria, the wording was changed from "assessments have been completed or will be performed" to "tests will be evaluated". A criterion was added that for patients who have received prior treatment with Spinraza® (nusinersen injection for intrathecal use) further therapy with Spinraza will be discontinued. **Conditions Not Recommended for Approval:** The criterion in this section stating to not approve Zolgensma for patients with complete paralysis of limbs and/or permanent ventilator dependence was split into two different criteria. The criterion in this section stating to not approve if the patient is currently receiving Spinraza was deleted as this is addressed in the approval conditions above.	06/18/2019
Annual Revision	The following changes was made: **Spinal Muscular Atrophy:** Criteria were added that if the patient is a premature neonate, full term gestational age of 39 weeks and 0 days has been met.	06/03/2020
Selected Revision	**Spinal Muscular Atrophy – Treatment:** In the duration of approval the wording "per lifetime" was added to describe the one-time dose. Regarding the criteria that the patient has not received Zolgensma, a notation that requires [verification by the prescriber] was added, as well as a Note to verify through claims history that the patient has not previously received Zolgensma AND, if no claim for Zolgensma is present, the prescriber must attest that the patient has not previously received Zolgensma. For the criterion that addresses if the patient has received prior treatment with Spinraza and that this therapy will be discontinued, wording was added that the prescriber attests to this. The requirement was added that for a patient who has received prior treatment with Evrysdi (risdiplam oral solution), that the prescriber attests that further therapy with Evrysdi will be discontinued. **Conditions Not Recommended for Approval:** The condition regarding paralysis of limbs was simplified from "The patient has complete paralysis of limbs to suggest advanced spinal muscular atrophy" to "Patient has Complete Paralysis of All Limbs". The condition regarding permanent ventilator dependence was simplified from "The patient has permanent ventilator dependence to suggest advanced spinal muscular atrophy" to "Patient has Permanent Ventilator Dependence."	08/12/2020
Selected Revision	**Spinal Muscular Atrophy – Treatment:** The criteria that requires the medication to be prescribed by or in consultation with a physician who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders was changed to "medication is prescribed by a physician who has consulted with or who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders". Also, regarding the criteria pertaining to not using Evrysdi concurrently, wording was added to include not only those who have received prior treatment with	11/18/2020

	Evrysdi, but also those "currently receiving" the therapy. Also, regarding the criteria pertaining to not using Spinraza after Zolgensma therapy, wording was added to include not only those who have received prior treatment with Spinraza, but also those "currently receiving" the therapy.	

PRIOR AUTHORIZATION POLICY

POLICY: Synagis Prior Authorization Policy
- Synagis® (palivizumab for intramuscular injection)

REVIEW DATE: 10/28/2020

OVERVIEW

Synagis, a respiratory syncytial virus (RSV) F protein inhibitor monoclonal antibody, is indicated for the **prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease**.[1] Safety and efficacy were established in children with bronchopulmonary dysplasia, infants with a history of premature birth, and children with hemodynamically significant congenital heart disease.

The safety and efficacy of Synagis for the treatment of RSV have not been established.[1] The recommended dose is 15 mg/kg intramuscularly once monthly (every 30 days). The first dose of Synagis should be administered prior to commencement of the RSV season and the remaining doses should be administered monthly throughout the RSV season.

RSV Seasonality

The CDC National Respiratory and Enteric Virus Surveillance System provides reports determining RSV seasonality, nationally and by region.[5] For the 2014 to 2017 seasons, median RSV onset occurred mid-October and lasted 31 weeks until early May. The median national peak occurred in early February. Many factors might influence national, regional, and county-level RSV activity, including social and demographic factors, population density, pollution, and climate.

Patterns of weekly RSV circulation in Florida are different from regional and national patterns.[2] Across the 2014 to 2017 seasons, the median onset for Florida was mid-September and the season continued through mid-April. Despite varying onset and offset dates of the RSV season in different regions of Florida, a maximum of five monthly doses will be adequate for qualifying infants for most RSV seasons in Florida.[3] Even if the first of five monthly doses is administered in July, protective serum concentrations of Synagis will be present for most infants and young children for at least 6 months and likely into February. More than five monthly doses are not recommended, despite the detection of a small number of cases of RSV infection outside this time window. A small number of sporadic RSV hospitalizations occur before or after the main season in many areas of the US, but maximum benefit from prophylaxis is derived during the peak of the season and not when the incidence of RSV hospitalization is low.

Guidelines

The AAP Policy Statement on the Updated Guidance for Synagis Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for RSV Infection was updated on August 1, 2014.[3] Additionally, the AAP Red Book was updated in 2018.[4] The AAP Red Book provides eligibility criteria for prophylaxis of high-risk infants and children in the following situations: preterm infants with chronic lung disease, infants with congenital heart disease (including those who undergo cardiac transplantation during the RSV season), preterm infants (before 29 weeks, 0 days' gestation) without chronic lung disease or congenital heart disease, children with anatomic pulmonary abnormalities or neuromuscular disorders, and immunocompromised children. Data are insufficient to justify a recommendation for routine use of

prophylaxis in patients with Down syndrome or among those with cystic fibrosis, unless other indications are present.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Synagis. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because five monthly doses of Synagis at 15 mg/kg per dose will provide more than 6 months of serum Synagis concentrations for most infants, administration of more than five monthly doses is not recommended within the continental US. Children who qualify for five monthly doses of Synagis should receive the first dose at the time of onset of the RSV season. For qualifying infants born during the RSV season, fewer than five monthly doses will be needed to provide protection until the RSV season ends in their region (maximum of five monthly doses).

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Synagis is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Chronic Lung Disease**. Approve for a maximum of 5 months during the RSV season if the patient meets one of the following criteria (A or B):
   - **A)** Patient is < 12 months of age at the start of the RSV season and meets the following criteria (i and ii):
     - **i.** Patient was born at < 32 weeks, 0 days gestation; AND
     - **ii.** Patient required > 21% oxygen for at least 28 days after birth; OR
   - **B)** Patient is ≥12 months of age but < 24 months of age at the start of the RSV season and meets the following criteria (i, ii, and iii):
     - **i.** Patient was born at < 32 weeks, 0 days gestation; AND
     - **ii.** Patient required > 21% oxygen for at least 28 days after birth; AND
     - **iii.** Patient has required medical therapy (i.e., supplemental oxygen, diuretic therapy, or chronic corticosteroid therapy) during the 6 months before the start of the second RSV season.

2. **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Congenital Heart Disease.** Approve for a maximum of 5 months during the RSV season if the patient meets the following criteria (A, B, and C):
   - **A)** Patient is < 12 months of age at the start of the RSV season; AND
   - **B)** According to the prescriber, patient meets one of the following criteria (i, ii, iii, or iv):
     - **i.** Patient is considered to have hemodynamically significant cyanotic CHD; OR
     - **ii.** Patient meets all of the following (a, b, and c):
       - **a)** Patient has acyanotic heart disease; AND
       - **b)** Patient is receiving medication to control heart failure; AND
       - **c)** Patient will require cardiac surgical procedures; OR
     - **iii.** Patient has moderate to severe pulmonary hypertension; OR
     - **iv.** Patient meets both of the following (a and b):
       - **a)** Patient has lesions that have been adequately corrected by surgery; AND

b) Patient continues to require medication for congestive heart failure; AND

C) Synagis is prescribed by or in consultation with a cardiologist or intensivist.

3. **Respiratory Syncytial Virus (RSV), Prevention in a Patient Born Prematurely.** Approve for a maximum of 5 months during the RSV season if the patient meets the following criteria (A and B):
   A) Patient is < 12 months of age at the start of the RSV season; AND
   B) Patient was born before 29 weeks, 0 days gestation (≤ 28 weeks, 6 days gestation).

Other Uses with Supportive Evidence

4. **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Anatomic Pulmonary Abnormalities or a Neuromuscular Disorder.** Approve for a maximum of 5 months during the RSV season if the patient meets the following criteria (A and B):
   A) Patient is < 12 months of age at the start of the RSV season; AND
   B) According to the prescriber, the patient's condition compromises the handling of respiratory secretions.

5. **Respiratory Syncytial Virus (RSV), Prevention in an Immunocompromised Patient.** Approve for a maximum of 5 months during the RSV season if the patient meets the following criteria (A, B, and C):
   Note: Examples of immunocompromised patients include those receiving chemotherapy and those with hematopoietic stem cell transplant or solid organ transplant.
   A) Patient is < 24 months of age at the start of the RSV season; AND
   B) According to the prescriber, the patient is/will be profoundly immunocompromised during the RSV season; AND
   C) Synagis is prescribed by or in consultation with an immunologist or an infectious diseases specialist.

6. **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Cardiac Transplant.** Approve for a maximum of 5 months during the RSV season if the patient meets the following criteria (A, B, and C):
   Note: A patient with cardiac transplant may also be immunocompromised. In a patient who does not meet criteria for cardiac transplant below, please see criterion 5 above (Respiratory Syncytial Virus [RSV], Prevention in an Immunocompromised Patient).
   A) Patient is < 24 months of age at the start of the RSV season; AND
   B) Patient has undergone or will undergo cardiac transplantation during the current RSV season; AND
   C) Synagis is prescribed by or in consultation is a cardiologist, intensivist, or transplant physician.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Synagis is not recommended in the following situations:

1. **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Cystic Fibrosis Who Does Not Meet Any of the Approval Criteria.** The AAP guidelines for RSV note that routine use of Synagis prophylaxis in patients with cystic fibrosis, including neonates diagnosed with cystic fibrosis by newborn screening, is not recommended unless other indications are present.[4] Available studies indicate the incidence of RSV hospitalization in children with cystic fibrosis is uncommon and unlikely to be different from children without cystic fibrosis.[3] A Cochrane Review identified one trial (presented in poster/abstract form) eligible for their review of Synagis prophylaxis in children with cystic fibrosis.[7]

In this prospective, double-blind, placebo-controlled, multi-center study, 14.1% vs. 14.9% of Synagis and placebo-treated patients, respectively were hospitalized within the first 6 months, and only one patient in each group was identified with RSV infection. There were no deaths in either group of patients during the first 6 months follow-up; this outcome was not reported at 12 months follow-up.

2. **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Down Syndrome <u>Who Does Not Meet Any of the Approval Criteria.</u>** Data suggest that children with Down syndrome have a slightly higher hospitalization rate for RSV, but the absolute number of hospitalizations is small, and a number of children with Down syndrome are at increased risk because of other qualifying risk factors (e.g., congenital heart disease, abnormalities of the respiratory tract, muscle dystonia).[2]

3. **Respiratory Syncytial Virus (RSV), Treatment of Disease.** There are limited data investigating Synagis for the treatment of established RSV infections. Passive antibody administration is not effective in treatment of RSV disease and is not approved or recommended for this indication.[2,6] If any infant or young child receiving monthly Synagis prophylaxis experiences a breakthrough RSV hospitalization, monthly prophylaxis should be discontinued because of the extremely low likelihood of a second RSV hospitalization (< 0.5%).[6]

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes. Added policy statement explaining RSV seasonality and removed explanations from individual criteria.	09/26/2018
Annual Revision	No criteria changes.	10/16/2019
Annual Revision	**Respiratory Syncytial Virus (RSV), Prevention in a Patient with Chronic Lung Disease:** The phrase "less than or equal to 1 year of age" was updated to "less than 12 months of age". The phrase "less than or equal to 2 years of age" was updated to "greater than or equal to 12 months of age but less than 24 months of age". **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Congenital Heart Disease:** The phrase "less than or equal to 1 year of age" was updated to "less than 12 months of age". The phrase "prescribing physician" was updated to "prescriber". **Respiratory Syncytial Virus (RSV), Prevention in a Patient Born Prematurely:** The phrase "less than or equal to 12 months of age" was updated to "less than 12 months of age". **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Anatomic Pulmonary Abnormalities or a Neuromuscular Disorder:** The phrase "less than or equal to 1 year of age" was updated to "less than 12 months of age". The phrase "prescribing physician" was updated to "prescriber". **Respiratory Syncytial Virus (RSV), Prevention in an Immunocompromised Patient:** Examples of immunocompromising conditions were moved to a note. Examples of "transplant" were clarified to include solid organ transplant and hematopoietic stem cell transplant. The phrase "prescribing physician" was updated to "prescriber". **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Cardiac Transplant:** The phrase "less than 2 years of age" was updated to "less than 24 months of age". **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Hematopoietic Stem Cell Transplant (Bone Marrow Transplant [BMT], Peripheral Blood, Placental or Cord Blood) Who Does Not Meet Any of the Approval Criteria:** This condition was removed from Conditions Not Recommended for Approval. **Wheezing, Prevention in Patients Who Do Not Meet Any of the Approval Criteria:** This condition was removed from Conditions Not Recommended for Approval.	10/28/2020

PRIOR AUTHORIZATION POLICY

POLICY: Testosterone Injectable Products

- Depo® - Testosterone (testosterone cypionate injection – Pfizer, generics)
- Delatestryl® (testosterone enanthate injection – Westward, generics only)
- Aveed™ (testosterone undecanoate injection – Endo Pharmaceuticals Inc.)
- Testopel® (testosterone pellet – Endo Pharmaceuticals Inc.)
- Xyosted™ (testosterone enanthate injection – Antares Pharma Inc.)

REVIEW DATE: 09/09/2020

OVERVIEW

Testosterone regimens can be administered orally, parenterally, or transdermally. Injectable testosterone replacement products include Depo-Testosterone (testosterone cypionate) for intramuscular (IM) use, Delatestryl (testosterone enanthate) for IM use, Aveed (testosterone undecanoate) for IM use, Xyosted (testosterone enanthate) for subcutaneous (SC) use, and Testopel (testosterone pellet) for SC implantation.[1-5] All the injectable agents are indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.[1-5] The prescribing information define those patients and/or conditions for which use of testosterone replacement products are indicated:

- **Primary hypogonadism (congenital or acquired):** testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchiectomy.

- **Hypogonadotropic hypogonadism (congenital or acquired):** gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation.

The diagnosis of male hypogonadism is based on both signs/symptoms and low testosterone levels. By restoring normal levels of testosterone, the replacement regimens correct symptoms of hypogonadism, which can include malaise, loss of muscle strength, depressed mood, and decreased libido.[6]

Testopel and Delatestryl (testosterone enanthate) are also indicated for **delayed puberty**.[2,3] Delatestryl (testosterone enanthate) [per the product labeling] may also be used secondarily in **women with advanced inoperable metastatic mammary cancer** that are 1 to 5 years postmenopausal.[2] The goal of therapy is ablation of ovaries. Per labeling, it also can be used in premenopausal women with breast cancer that have benefited from oophorectomy and are considered to have hormone-responsive tumors.

Guidelines

- **Hypogonadism:** Guidelines from the American Urological Association (2018) note that clinicians should use a total testosterone level below 300 ng/dL as a reasonable cut-off in support of the diagnosis of low testosterone.[7] The guidelines additionally note that a diagnosis of low testosterone should be made only after two total testosterone measurements are taken on separate occasions with both conducted in an early morning fashion and that a clinical diagnosis should be made when patients have low testosterone levels combined with signs and symptoms. The Endocrine Society guidelines on testosterone therapy in men with hypogonadism (2018) recommend diagnosing hypogonadism in men with symptoms and signs of testosterone deficiency and unequivocally and consistently low serum total testosterone and/or free testosterone concentrations (when indicated).[8]
- **Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Female-To-Male (FTM) Gender Reassignment (i.e., Endocrinologic Masculinization):** A clinical practice guideline published by the Endocrine Society (2017), recommends that, prior to initiation of hormonal therapy, the treating endocrinologist should confirm the diagnostic criteria of gender dysphoria/gender incongruence and the criteria for the endocrine phase of gender transition.[9] The clinical should also evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment. Guidelines mention that clinicians can use either parenteral or transdermal preparations to achieve appropriate testosterone values.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of injectable testosterone. All approvals are provided for the duration noted below. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: males are defined as individuals with the biological traits of a male, regardless of the individual's gender identity or gender expression; females are defined as individuals with the biological traits of a female, regardless of the individual's gender identity or gender expression. Because of the specialized skills required for evaluation and diagnosis of some patients treated with testosterone, certain approval requires testosterone to be prescribed by or in consultation with a physician who specializes in the conditions being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of injectable testosterone is recommended in those who meet the following criteria:

FDA-Approved Indications

262. Hypogonadism (Primary or Secondary) in Males* [Testicular Hypofunction/Low Testosterone with Symptoms]. Approve for 1 year if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve in patients with hypogonadism as confirmed by the following criteria (i, ii, and iii):

- **i.** Patient has had persistent signs and symptoms of androgen deficiency (pre-treatment); AND
  Note: Signs and symptoms of androgen deficiency include depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, and loss of libido.
- **ii.** Patient has had two pre-treatment serum testosterone (total or bioavailable) measurements, each taken in the morning, on two separate days; AND
- **iii.** The two serum testosterone levels are both low, as defined by the normal laboratory reference values.

B) Patients Continuing Therapy. Approve if the patient meets the following criteria (i and ii):

- **i.** Patient has had persistent signs and symptoms of androgen deficiency (pre-treatment); AND
  Note: Signs and symptoms of androgen deficiency include depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, and loss of libido.
- **ii.** Patient has had at least one pre-treatment serum testosterone (total or bioavailable) level, which was low, as defined by the normal laboratory reference values.

* Refer to the Policy Statement

Note: The pre-treatment timeframe refers to sign and symptoms of androgen deficiency and serum testosterone levels prior to the initiation of any testosterone therapy.

263. Delayed Puberty or Induction of Puberty in Males* 14 years of Age or Older. Approve Depo-Testosterone (testosterone cypionate), Delatestryl (testosterone enanthate), or Testopel for 6 months.

*Refer to the Policy Statement

264. Breast Cancer in Females*. Approve Delatestryl (testosterone enanthate) injection in women for 6 months if it is prescribed by or in consultation with an oncologist.

*Refer to the Policy Statement.

Other Uses with Supportive Evidence

265. Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Female-to-Male (FTM) Gender Reassignment (i.e., Endocrinologic Masculinization). Approve for 1 year if prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of transgender patients.

Note: For patients who have undergone gender reassignment, use this FTM criterion for hypogonadism indication.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of injectable testosterone is not recommended in the following situations:

266. To Enhance Athletic Performance. Injectable testosterone products are not recommended for approval because this indication is excluded from coverage in a typical pharmacy benefit.

267. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
Selected Revision	Added Xyosted subcutaneous (testosterone enanthate) to the policy. This product is added as an approved product for hypogonadism (primary or secondary) in males and for female-to-male gender reassignment with the same approval criteria as already in the policy.	11/07/2018
Annual Revision	**Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Female-To-Male (FTM) Gender Reassignment** (i.e., Endocrinologic Masculinization) approval condition was changed to as listed; previously, listed as "Female-To-Male (FTM) Gender Reassignment (i.e., Endocrinologic Masculinization)." **Breast Cancer in Females** approval condition was changed to as listed; previously, listed as "Palliative Treatment of Inoperable Metastatic Breast Cancer in Females."	08/28/2019
Annual Revision	**Hypogonadism**: Examples of signs and symptoms of androgen deficiency were placed as a Note.	09/09/2020

PRIOR AUTHORIZATION POLICY

POLICY: Testosterone (Oral, Topical, and Nasal) Prior Authorization Policy

Oral Testosterone Products

- Jatenzo® (testosterone undecanoate capsules – Clarus Therapeutics, Inc.)
- Striant™ (testosterone buccal system, mucoadhesive – Endo Pharmaceuticals, Inc.) [obsolete]

Transdermal Patch

- Androderm® (testosterone transdermal system [2,4 mg/day] – Allergan)

Transdermal Gels

- AndroGel® (testosterone 1% gel, 1.62% gel – AbbVie, Inc., generics)
- Fortesta™ (testosterone 2% gel – Endo Pharmaceuticals, Inc., generics)
- Testim® (testosterone 1% gel – Endo Pharmaceuticals, Inc., generics)
- Vogelxo™ (testosterone 1% gel – Upsher-Smith Laboratories, generics)

Transdermal Solution

- Axiron™ (testosterone 2% solution – Lilly USA, LLC, generics only)

Nasal Gel

- Natesto™ (testosterone nasal gel – Aytu Bioscience, Inc)

REVIEW DATE: 09/09/2020

OVERVIEW

The oral, topical, and nasal testosterone replacement products are all indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.[1-10] The prescribing information for the FDA-approved products define those patients and/or conditions for which use of testosterone replacement products are indicated:

- **Primary hypogonadism (congenital or acquired):** testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal.
- **Hypogonadotropic hypogonadism (congenital or acquired):** gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations, but have gonadotropins in the normal or low range.

The diagnosis of male hypogonadism is based on both signs/symptoms and low testosterone levels. By restoring normal levels of testosterone, the replacement regimens correct symptoms of hypogonadism, which can include malaise, loss of muscle strength, depressed mood, and decreased libido.[12]

Guidelines

- **Hypogonadism:** Guidelines from the American Urological Association (2018) note that clinicians should use a total testosterone level below 300 ng/dL as a reasonable cut-off in support of the diagnosis of low testosterone.[13] The guidelines additionally note that a diagnosis of low testosterone should be made only after two total testosterone measurements are taken on separate occasions with both conducted in an early morning fashion and that a clinical diagnosis should be made when patients have low testosterone levels combined with signs and symptoms. The Endocrine Society guidelines on testosterone therapy in men with hypogonadism (2018) recommend diagnosing hypogonadism in men with symptoms and signs of testosterone deficiency and unequivocally and consistently low serum total testosterone and/or free testosterone concentrations (when indicated).[11]
- **Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Female-To-Male (FTM) Gender Reassignment (i.e., Endocrinologic Masculinization):** A clinical practice guideline published by the Endocrine Society (2017), recommends that, prior to initiation of hormonal therapy, the treating endocrinologist should confirm the diagnostic criteria of gender dysphoria/gender incongruence and the criteria for the endocrine phase of gender transition.[14] The clinician should also evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment. Guidelines mention that clinicians can use either parenteral or transdermal preparations to achieve appropriate testosterone values.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of oral, topical and nasal testosterone products. In the approval indications, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: males are defined as individuals with the biological traits of a male, regardless of the individuals' gender identity or gender expression. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of some patients treated with testosterone, certain approval requires testosterone to be prescribed by or in consultation with a physician who specializes in the conditions being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of oral, topical, and nasal testosterone products is recommended in those who meet the following criteria:

FDA-Approved Indications

266. Hypogonadism (Primary or Secondary) in Males* [Testicular Hypofunction/Low Testosterone with Symptoms]. Approve for 1 year if the patient meets the following criteria (A or B):

Note: The pre-treatment timeframe refers to signs and symptoms of androgen deficiency and serum testosterone levels prior to the initiation of any testosterone therapy.

A) Initial Therapy: Patients with hypogonadism as confirmed by the following criteria (i, ii, and iii):
- **i.** Patient has had persistent signs and symptoms of androgen deficiency (pre-treatment); AND
  Note: Signs and symptoms of androgen deficiency include depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, and loss of libido.
- **ii.** Patient has had two pre-treatment serum testosterone (total or bioavailable) measurements, each taken in the morning, on two separate days; AND
- **iii.** The two serum testosterone levels are both low, as defined by the normal laboratory reference values.

B) Patients Continuing Therapy. Approve if the patient meets the following criteria (i and ii):
- **i.** Patient has had persistent signs and symptoms of androgen deficiency (pre-treatment); AND
  Note: Signs and symptoms of androgen deficiency include depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, and loss of libido.
- **ii.** Patient has had at least one pre-treatment serum testosterone (total or bioavailable) level, which was low, as defined by the normal laboratory reference values.

*Refer to the Policy Statement.

Other Uses with Supportive Evidence

267. Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Female-To-Male (FTM) Gender Reassignment (i.e., Endocrinologic Masculinization). Approve for 1 year if prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of transgender patients.

Note: For patients who have undergone gender reassignment, use this FTM criterion for hypogonadism indication.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of oral, topical, and nasal testosterone products is not recommended in the following situations:

268. To Enhance Athletic Performance. Topical testosterone products are not recommended for approval because this indication is excluded from coverage in a typical pharmacy benefit.

269. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	08/15/2018
Annual Revision	Jatenzo (testosterone oral capsule) was added to the policy with the same criteria applied as those for the other testosterone (topical and nasal) products. Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Female-To-Male (FTM) Gender Reassignment (i.e., Endocrinologic Masculinization) approval condition was changed to as listed; previously, listed as "Female-To-Male (FTM) Gender Reassignment (i.e., Endocrinologic Masculization)."	08/28/2019
Annual revision	**Hypogonadism:** Examples of signs and symptoms of androgen deficiency were placed as a Note.	09/09/2020

PRIOR AUTHORIZATION POLICY

POLICY: Thrombocytopenia – Doptelet Prior Authorization Policy

- Doptelet® (avatrombopag tablets for oral use – Dova/AkaRx)

REVIEW DATE: 03/17/2021

OVERVIEW

Doptelet, a thrombopoietin receptor agonist, is indicated for the treatment of:[1]

- **Immune thrombocytopenia (ITP)**, chronic, in adults who have had an insufficient response to a previous treatment.
- **Chronic liver disease,** adults with thrombocytopenia who are scheduled to undergo a procedure.

For chronic ITP, Doptelet should be discontinued if the platelet count does not increase to $\geq 50 \times 10^9$/L within 4 weeks at the maximum dose of 40 mg once daily (QD). The safety and efficacy of Doptelet have not been established in pediatric patients. For chronic liver disease in patients undergoing a procedure, Doptelet is given as a 5-day course beginning 10 to 13 days before the scheduled procedure. In general, patients in the pivotal studies had a platelet count $< 50 \times 10^9$/L.

Guidelines

In 2019 the American Society of Hematology updated guidelines for ITP.[4] Doptelet is not addressed specifically, but there are several recommendations. For adults with ITP for at least 3 months who are corticosteroid-dependent or unresponsive to corticosteroid, a thrombopoietin receptor agonist (either Promacta® [eltrombopag tablets and oral suspension] or Nplate® [romiplostim injection for subcutaneous use]) or a splenectomy are recommended. In children with newly diagnosed ITP who have non-life-threatening mucosal bleeding, corticosteroids are recommended. For children who have non-life-threatening mucosal bleeding and do not respond to first-line treatment, thrombopoietin receptor agonists are recommended. Other treatment options in children and adults include intravenous immunoglobulin, anti-D immunoglobulin, and rituximab.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Doptelet. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Doptelet as well as the monitoring required for adverse events and long-term efficacy, approval may require Doptelet to be prescribed by or in consultation with a physician who specializes in the condition being treated in certain indications.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Doptelet is recommended in those who meet the following criteria:

FDA-Approved Indications

~~95.~~92. **Chronic Immune Thrombocytopenia.** Approve if the patient meets the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets all of the following (i, ii, iii, and iv):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient meets one of the following (a or b):
  - **a)** Patient has a platelet count < 30 x 10^9/L (< 30,000/mcL); OR
  - **b)** Patient meets both of the following [(1) and (2)]:
    - **(1)** Patient has a platelet count < 50 x 10^9/L (< 50,000/mcL); AND
    - **(2)** According to the prescriber, the patient is at an increased risk of bleeding; AND
- **iii.** Patient meets one of the following (a or b):
  - **a)** Patient has tried at least one other therapy; OR
    Note: Examples of therapies are systemic corticosteroids, intravenous immunoglobulin, anti-D immunoglobulin, Promacta (eltrombopag tablets and oral suspension), Nplate (romiplostim injection for subcutaneous use), Tavalisse (fostamatinib tablets), and rituximab.
  - **b)** Patient has undergone splenectomy; AND
- **iv.** The medication is prescribed by or in consultation with a hematologist; OR

B) Continuation of Therapy. Approve for 1 year if the patient meets both of the following criteria: (i and ii):
- **i.** According to the prescriber, the patient demonstrates a beneficial clinical response; AND
  Note: A beneficial response can include increased platelet counts, maintenance of platelet counts, and/or a decreased frequency of bleeding episodes.
- **ii.** Patient remains at risk for bleeding complications.

~~96.~~93. **Thrombocytopenia in a Patient with Chronic Liver Disease.** Approve for 5 days if the patient meets the following criteria (A, B, and C):

42. Patient is ≥ 18 years of age; AND

43. Patient has a current platelet count < 50 x 10^9/L (< 50,000/mcL); AND

44. Patient is scheduled to undergo a procedure within 10 to 13 days after starting Doptelet therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Doptelet is recommended in the following situations:

315. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

62. Doptelet® tablets [prescribing information]. Durham, NC: AkaRx/Dova Pharmaceuticals; October 2020.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Chronic Immune Thrombocytopenia:** Criteria were added based on the new indication for use in adults with chronic immune thrombocytopenia in patients who have had an insufficient response to a previous treatment. **Conditions Not Recommended for Approval:** The condition of chronic immune thrombocytopenia was removed as it is now an FDA-approved indication.	07/03/2019
Early Annual Revision	**Chronic Immune Thrombocytopenia:** Criteria were divided into Initial Therapy and Continuation of Therapy. For Initial Therapy, the approval duration is for 3 months. Criteria were added that the patient has a platelet count < 30 x 10^9/L (< 30,000/µL) or that the patient had a platelet count < 50 x 10^9/L (< 50,000/µL) and according to the prescriber the patient is at an increased risk of bleeding. Also, regarding the requirement of a trial of at least one therapy, the word "systemic" was added before the word corticosteroids. Continuation of therapy is approved for 1 year in duration if, according to the prescriber, the patient demonstrates a beneficial clinical response (e.g., increase in platelet counts); AND the patient remains at risk for bleeding complications.	03/11/2020
Annual Revision	**Chronic Immune Thrombocytopenia:** For the Continuation of Therapy criteria, the example of increased platelet counts to denote an example of a beneficial response was moved from an example within the criteria to a Note: Also, maintenance of platelet counts, and/or a decreased frequency of bleeding episodes were also added as examples to the Note as well.	03/17/2021

PRIOR AUTHORIZATION POLICY

POLICY: Thrombocytopenia – Mulpleta Prior Authorization Policy

- Mulpleta® (lusutrombopag tablets for oral use – Shionogi/Quotient)

REVIEW DATE: 03/11/2020

OVERVIEW

Mulpleta is a thrombopoietin receptor agonist (TPO-RA) indicated for the treatment of thrombocytopenia in adults with chronic liver disease who are scheduled to undergo a procedure.[1] Begin Mulpleta dosing 8 to 14 days before the scheduled procedure. The recommended dose is 3 mg once daily (QD) with or without food for 7 days. Patients should undergo their procedure 2 to 8 days after the last Mulpleta dose. The safety and efficacy in pediatric patients have not been established.

Clinical Efficacy

The efficacy of Mulpleta for the treatment of thrombocytopenia in patients with chronic liver disease who were scheduled to undergo a procedure was established in two randomized, double-blind, placebo-controlled trials (L-PLUS 1 [n = 97] and L-PLUS 2 [n = 215]).[1-3] Patients with chronic liver disease who were to be undergoing an invasive procedure were required to have a platelet count < 50 x 10^9/L to participate. The median patient age was 60 years (range, 18 to 88 years). In L-PLUS 1, the major efficacy outcome was the proportion of patients who did not require a platelet transfusion prior to the primary invasive procedure. In L-PLUS 2, the major efficacy outcome was the proportion of patients who did not require a platelet transfusion before the procedure and no rescue therapy for bleeding (i.e., platelet preparations, other blood preparations [including red blood cells and plasma, volume expanders]) from randomization through 7 days following the primary invasive procedure. Other endpoints were also assessed. In L-PLUS 1, 78% of patients given Mulpleta (n = 38/49) compared with 13% of patients randomized to placebo (n = 6/48) did not require a platelet transfusion prior to the invasive procedure (P < 0.0001). In L-PLUS 2, the proportion of patients not requiring a platelet transfusion prior to the invasive procedure or rescue therapy for bleeding from randomization through 7 days following the invasive procedure was 65% in the Mulpleta group vs. 29% (n = 31/107) in the placebo group (P < 0.0001).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Mulpleta. Approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mulpleta is recommended in those who meet the following criteria:

FDA-Approved Indication

~~97.~~94. **Thrombocytopenia in Patients with Chronic Liver Disease.** Approve for 7 days if the patient meets the following criteria (A, B and C):

45. Patient is ≥ 18 years of age; AND

46. Patient has a current platelet count < 50 x 10^9/L (< 50,000/µL); AND

47. Patient is scheduled to undergo a procedure within 8 to 14 days after starting Mulpleta therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Mulpleta is recommended in those who meet the following criteria:

316. Chronic Immune Thrombocytopenia. Data are not available regarding use of Mulpleta in patients with persistent and chronic ITP. Many other agents are FDA-approved for this condition and are recommended in standard guidelines and have established efficacy and safety.[4]

317. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	Not applicable.	08/01/2018
Annual Revision	No criteria changes.	07/03/2019
Early Annual Revision	No criteria changes.	03/11/2020

PRIOR AUTHORIZATION POLICY

POLICY: Thrombocytopenia – Nplate Prior Authorization Policy

- Nplate® (romiplostim injection for subcutaneous use – Amgen)

REVIEW DATE: 03/17/2021

OVERVIEW

Nplate, a thrombopoietin receptor agonist, is indicated for the treatment of:[1]

- **Hematopoietic Syndrome of Acute Radiation Syndrome (HS-ARS)**, to increase survival in adults and pediatric patients (including term neonates) acutely exposed to myelosuppressive doses of radiation.
- **Immune thrombocytopenia (ITP), in adults** who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.
- **Immune thrombocytopenia (ITP), in pediatric patients ≥ 1 year of age** with ITP for at least 6 months who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Nplate should only be utilized in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. Nplate should not be used in an attempt to normalize platelet counts.

Guidelines

Nplate is mentioned in guidelines related to ITP, as well as in myelodysplastic syndrome (MDS).

- **Immune Thrombocytopenia:** The American Society of Hematology updated guidelines for ITP (2019). For adults with ITP for at least 3 months who are corticosteroid-dependent or unresponsive to corticosteroid, a thrombopoietin receptor agonist (Nplate or Promacta® [eltrombopag tablets and oral suspension]) or a splenectomy are recommended.[2] In children with newly diagnosed ITP who have non-life-threatening mucosal bleeding, corticosteroids are recommended. For children who have non-life-threatening mucosal bleeding and do not respond to first-line treatment thrombopoietin receptor agonists are recommended.
- **Myelodysplastic Syndrome (MDS):** National Comprehensive Cancer Network recommendations regarding MDS (version 3.2021 – January 15, 2021) state to consider treatment with a thrombopoietin receptor agonist in patients with lower-risk MDS who have severe or life-threatening thrombocytopenia.[3] Data are available that describe the use of Nplate in patients with MDS.[4-13] The data with Nplate are discussed noting an increased rate of platelet response and decreased overall bleeding events among patients with low to intermediate risk MDS.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Nplate. All approvals are provided for the duration noted below. Regarding the approval duration of one dose, the approval is for 30 days, which is an adequate duration for the patient to receive one dose. Because of the specialized skills required for evaluation and diagnosis of patients treated with Nplate as well as the monitoring required for adverse events and efficacy, approval for some indications requires Nplate to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nplate is recommended in those who meet the following criteria:

FDA-Approved Indication

47. Hematopoietic Syndrome of Acute Radiation Syndrome. Approve for one dose if the patient has been acutely exposed to myelosuppressive doses of radiation.

48. Immune Thrombocytopenia. Approve if the patient meets one of the following criteria (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets all of the following criteria (i, ii, and iii):

i. Patient meets one of the following (a or b):

a) Patient has a platelet count < 30 x 10^9/L (< 30,000/mcL); OR

b) Patient meets both of the following [(1) and (2)]:

(1) Patient has a platelet count < 50 x 10^9/L (< 50,000/mcL); AND

(2) According to the prescriber the patient is at an increased risk of bleeding; AND

ii. Patient meets one of the following (a or b):

a) Patient has tried at least one other therapy; OR

Note: Examples of therapies are systemic corticosteroids, intravenous immunoglobulin, anti-D immunoglobulin, Promacta® (eltrombopag tablets and oral suspension), Tavalisse™ (fostamatinib tablets), Doptelet® (avatrombopag tablets), or ritixumab.

b) Patient has undergone splenectomy; AND

iii. Medication is prescribed by or in consultation with a hematologist; OR

B) Continuation of Therapy. Approve for 1 year if the patient meets both of the following criteria: (i and ii):

iii. According to the prescriber the patient demonstrates a beneficial clinical response; AND

Note: A beneficial response can include increased platelet counts, maintenance of platelet counts, and/or a decreased frequency of bleeding episodes.

iv. Patient remains at risk for bleeding complications.

Other Uses with Supportive Evidence

2. Thrombocytopenia in Myelodysplastic Syndrome (MDS). Approve if the patient meets one the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets all of the following criteria (i, ii, and iii):

i. Patient has low- to intermediate-risk myelodysplastic syndrome; AND

ii. Patient meets one of the following (a or b):

a) Patient has a platelet count < 30 x 10^9/L (< 30,000/mcL); OR

b) Patient meets both of the following [(1) and (2)]:

(1) Patient has a platelet count < 50 x 10^9/L (< 50,000/mcL); AND

(2) According to the prescriber the patient is at an increased risk for bleeding; AND

iii. Medication is prescribed by or in consultation with a hematologist or an oncologist; OR

B) Continuation of Therapy. Approve for 1 year if the patient meets both of the following criteria (i and ii):

i. According to the prescriber the patient demonstrates a beneficial clinical response; AND

Note: A beneficial response can include increased platelet counts, maintenance of platelet counts, and/or decreased frequency of bleeding episodes.

ii. Patient remains at risk for bleeding complications.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nplate is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	The following criteria changes were made: **1. Chronic Immune Thrombocytopenia:** The approval duration was changed from 3 years to 1 year. Doptelet was added to the list of alternatives that count towards the criteria that requires a trial of one other therapy.	07/03/2019
Early Annual Revision	The following criteria changes were made: 1. **Chronic Immune Thrombocytopenia:** Criteria were divided into Initial Therapy and Continuation of Therapy. For Initial Therapy, the approval duration was changed from 1 year to 3 months. Criteria were added that the patient has a platelet count < 30 x 10^9/L (< 30,000/µL) or that the patient had a platelet count < 50 x 10^9/L (< 50,000/µL) and, according to the prescriber, the patient is at an increased risk of bleeding. Also, regarding the requirement of a trial of at least one therapy, the descriptor "systemic" was added in reference to corticosteroids. Continuation of therapy is approved for a 1-year duration if, according to the prescriber, the patient demonstrates a beneficial clinical response (e.g., increase in platelet counts) and the patient remains at risk for bleeding complications. **2. Thrombocytopenia in Myelodysplastic Syndrome:** Criteria were divided into Initial Therapy and Continuation of Therapy. For Initial Therapy, the approval duration was changed from 1 year to 3 months. Criteria were added that the patient has a platelet count < 30 x 10^9/L (< 30,000/µL) or that the patient had a platelet count < 50 x 10^9/L (< 50,000/µL) and, according to the prescriber, the patient is at an increased risk of bleeding. Previously, the criteria just required that the patient had clinically significant thrombocytopenia (e.g., low platelet counts [< 30 x 10^9/L {< 30,000/µL} {pretreatment}]; is platelet transfusion-dependent; active bleeding, and/or a history of bleeding at low platelet counts). Continuation of therapy is approved for a 1-year if, according to the prescriber, the patient demonstrates a beneficial clinical response (e.g., increase in platelet counts) and the patient remains at risk for bleeding complications).	03/11/2020
Annual Revision	The following changes were made: 1. **Hematopoietic Syndrome of Acute Radiation Syndrome:** Criteria were added for this recently FDA-approved use to approve for one dose if the patient has been acutely exposed to myelosuppressive doses of radiation. Also, a Note was added to the Policy Statement that approval is for 30 days which is an adequate duration for the patient to receive one dose. 2. **Immune Thrombocytopenia:** The word "Chronic" was removed from the indication of use. For the Continuation of Therapy criteria, the example of increased platelet counts to denote an example of a beneficial response was moved from an example within the criteria to a Note. Also, maintenance of platelet counts, and/or a decreased frequency of bleeding episodes were also added as examples to the Note as well. **3. Thrombocytopenia in Myelodysplastic Syndrome:** For the Continuation of Therapy criteria, the example of increased platelet counts to denote an example of a beneficial response was moved from an example within the criteria to a Note. Also, maintenance of platelet counts, and/or a decreased frequency of bleeding episodes were also added as examples to the Note as well.	03/17/2021

FDA – Food and Drug Administration.

PRIOR AUTHORIZATION POLICY

POLICY: Thrombocytopenia – Promacta Prior Authorization Policy

- Promacta® (eltrombopag tablets and oral suspension – Novartis)

REVIEW DATE: 03/17/2021

OVERVIEW

Promacta, a thrombopoietin receptor agonist, is indicated for the treatment of:[1]

- **Aplastic anemia**, severe, in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients ≥ 2 years of age as well as for patients who have had an insufficient response to immunosuppressive therapy.
- **Chronic hepatitis C, treatment of thrombocytopenia** to allow the initiation and maintenance of interferon-based therapy.
- **Immune thrombocytopenia (ITP), in adult and pediatric patients ≥ 1 year of age** with persistent or chronic ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding.

For patients with refractory severe aplastic anemia, if no hematologic response has occurred after 16 weeks of treatment with Promacta, discontinue therapy. For ITP, Promacta should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of therapy with Promacta at the maximum daily dose of 75 mg. Use Promacta only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy.[1] The safety and efficacy of Promacta have not been established in combination with direct-acting antiviral agents used without interferon for the treatment of chronic hepatitis C infection. For the management of chronic hepatitis C, Promacta should be stopped upon discontinuation of antiviral treatment futility.

Guidelines

Promacta is addressed in several guidelines.

- **Aplastic Anemia:** Guidelines for the diagnosis and management of adult aplastic anemia are also available from the British Society for Standards in Hematology (2016).[2] Immunosuppressive therapy is recommended first-line for non-severe aplastic anemia in patients requiring treatment, severe or very severe aplastic anemia in patients who lack a matched sibling donor, and severe or very severe aplastic anemia in patients > 35 to 50 years of age. Other immunosuppressive recommended have been studied (e.g., mycophenolate mofetil, sirolimus, corticosteroids) but expertise should be provided prior to consideration of such agents. Hematopoietic stem cell transplantation (HSCT) is also recommended in certain circumstances. Promacta is an option is some clinical scenarios (e.g., heavily pre-treated patients, those unsuitable for HSCT).
- **Immune Thrombocytopenia (ITP):** The 2019 the American Society of Hematology updated guidelines for ITP.[3] There are several recommendations. For adults with ITP for at least 3 months who are corticosteroid-dependent or unresponsive to corticosteroid, a thrombopoietin receptor agonist (Promacta or Nplate® [romiplostim injection for subcutaneous use]) or a splenectomy are recommended. In children with newly diagnosed ITP who have non-life-threatening mucosal bleeding, corticosteroids are recommended. For children who have non-life-threatening mucosal bleeding and do not respond to first-line treatment, thrombopoietin receptor agonists are recommended. Other treatment options in children and adults include intravenous immunoglobulin, anti-D immunoglobulin, and rituximab.
- **Myelodysplastic Syndrome (MDS):** Current recommendations from the National Comprehensive Cancer Network for MDS (version 3.2021 – January 15, 2021) state to consider treatment with a thrombopoietin receptor agonist in patients with lower-risk MDS who have severe or life-threatening thrombocytopenia.[4] The data with Promacta are discussed noting increased rate of platelet response and decreased overall bleeding events among patients with low- to intermediate-risk MDS. Other data are also available that describe the use of Promacta in patients with MDS.[5-7]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Promacta. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Promacta as well as the monitoring required for adverse events and efficacy, approval requires Promacta to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Promacta is recommended in those who meet the following criteria:

FDA-Approved Indications

49. Aplastic Anemia. Approve if the patient meets one of the following (A or B):

A. Initial Therapy. Approve for 4 months if the patient meets the following criteria (i, ii, and iii):

i. Patient has low platelet counts at baseline (pretreatment); AND
Note: An example of a low platelet count is < 30 x 10^9/L (< 30,000/mcL).

ii. Patient meets one of the following (a or b):

a) Patient had tried at least one immunosuppressant therapy; OR
Note: Examples of therapies are cyclosporine, Atgam® (lymphocyte immune globulin, anti-thymocyte globulin [equine] sterile solution for intravenous use only), mycophenolate moefetil, or sirolimus.

b) Patient will be using Promacta in combination with standard immunosuppressive therapy; AND
Note: Examples of therapies are cyclosporine, Atgam® (lymphocyte immune globulin, anti-thymocyte globulin [equine] sterile solution for intravenous use only), mycophenolate moefetil, or sirolimus.

iii. Promacta is prescribed by or in consultation with a hematologist; OR

B. Continuation of Therapy. Approve for 1 year if, according to the prescriber, the patient demonstrates a beneficial clinical response.
Note: Examples include increases in platelet counts, reduction in red blood cell transfusions, hemoglobin increase, and/or absolute neutrophil count increase.

50. Immune Thrombocytopenia. Approve if the patient meets one the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets all of the following (i, ii, and iii):

i. Patient meets one of the following (a or b):

a) Patient has a platelet count < 30 x 10^9/L (< 30,000/mcL); OR

b) Patient meets both of the following [(1) and (2)]:

(1) Patient has a platelet count < 50 x 10^9/L (< 50,000/mcL); AND

(2) According to the prescriber the patient is at an increased risk for bleeding; AND

ii. Patient meets one of the following (a or b):

a) Patient has tried at least one other therapy; OR
Note: Examples of therapies are systemic corticosteroids, intravenous immunoglobulin, anti-D immunoglobulin, Nplate (romiplostim injection for subcutaneous use), Tavalisse (fostamatinib tablets), Doptelet (avatrombopag tablets), or rituximab.

b) Patient has undergone splenectomy; AND

iii. The medication is prescribed by, or in consultation with, a hematologist; OR

B) Continuation of Therapy. Approve for 1 year if the patient meets both of the following criteria (i and ii):

i. According to the prescriber, the patient demonstrates a beneficial clinical response; AND

Note: A beneficial response can include increased platelet counts, maintenance of platelet counts, and/or a decreased frequency of bleeding episodes.

ii. Patient remains at risk for bleeding complications.

51. Thrombocytopenia in a Patient with Chronic Hepatitis C. Approve Promacta for 1 year if the patient meets the following criteria (A, B, and C):

A) Patient has low platelet counts at baseline (pretreatment); AND
Note: An example of a low platelet count is < 75 x 10^9/L (< 75,000/mcL).

B) Patient will be receiving interferon-based therapy for chronic hepatitis C; AND
Note: Examples of therapies are pegylated interferon (Pegasys® [peginterferon alfa-2a injection], PegIntron® [peginterferon alfa-2b injection]), or Intron A® (interferon alfa-2b).

C) The medication is prescribed by or in consultation with either a gastroenterologist, a hepatologist, or a physician who specializes in infectious disease.

Other Uses with Supportive Evidence

4. Thrombocytopenia in Myelodysplastic Syndrome. Approve if the patient meets one of the following (A or B):

B) Initial Therapy. Approve for 3 months if the patient meets the following criteria (i, ii, and iii):

a. Patient has low- to intermediate-risk myelodysplastic syndrome; AND

b. Patient meets one of the following (a or b):

a) Patient has a platelet count < 30 x 10^9/L (< 30,000/mcL); OR

b) Patient meets one of the following [(1) and (2)]:

i. Patient has a platelet count < 50 x 10^9/L (< 50,000/mcL); AND

ii. According to the prescriber, the patient is at an increased risk for bleeding; AND

c. The medication is prescribed by or in consultation with a hematologist or an oncologist; OR

B) Continuation of Therapy. Approve for 1 year if the patient meets both of the following criteria (i and ii):

iii. According to the prescriber the patient demonstrates a beneficial clinical response; AND
Note: A beneficial response can include increased platelet counts, maintenance of platelet counts, and/or decreased frequency of bleeding episodes.

iv. Patient remains at risk for bleeding complications.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Promacta is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Chronic Immune Thrombocytopenia:** Doptelet was added to the list of alternatives that count towards the criteria that requires a trial of one other therapy. The approval duration was changed from 3 years to 1 year.	07/03/2019
Early Annual Revision	**Aplastic Anemia:** Criteria were divided into Initial Therapy and continuation of therapy. Initial approval duration was changed from 1 year to 4 months. Continuation of Therapy were added that approves for 1 year if, according to the prescriber, the patient demonstrates a beneficial clinical response. A Note was added that cites examples of a clinical response which includes increases in platelet counts, reduction in red blood cell transfusions, hemoglobin increase, and/or absolute neutrophil count increase. **Chronic Immune Thrombocytopenia:** Criteria were divided into Initial Therapy and Continuation of Therapy. For Initial Therapy, the approval duration was changed from 1 year to 3 months. Criteria were added that the patient has a platelet count < 30 x 10^9/L (< 30,000/µL) or that the patient has a platelet count < 50 x 10^9/L (< 50,000/µL) and according to the prescriber the patient is at an increased risk of bleeding. Also, regarding the requirement of a trial of at least one therapy, the word "systemic" was added before the word corticosteroids. Continuation of therapy is approved for a 1-year duration if, according to the prescriber, the patient demonstrates a beneficial clinical response (e.g., increase in platelet counts) AND the patient remains at risk for bleeding complications. **Thrombocytopenia in Myelodysplastic Syndrome:** Criteria were divided into Initial Therapy and Continuation of Therapy. For Initial Therapy the approval duration was changed from 1 year to 3 months. Criteria were added that the patient has a platelet count < 30 x 10^9/L (< 30,000/µL) or that the patient had a platelet count < 50 x 10^9/L (< 50,000/µL) and, according to the prescriber, the patient is at an increased risk of bleeding. Previously, the criteria just required that the patient had clinically significant thrombocytopenia (e.g., low platelet counts [< 30 x 10^9/L {< 30,000/µL} {pretreatment}]; is platelet transfusion-dependent; active bleeding, and/or a history of bleeding at low platelet counts). Continuation of therapy is approved for a 1-year duration if the, according to the prescriber, the patient demonstrates a beneficial clinical response (e.g., increase in platelet counts) and the patient remains at risk for bleeding complications.	03/11/2020
Annual Revision	**Aplastic Anemia:** The provided value as an example of a low platelet count was moved from the criteria to a Note. **Immune Thrombocytopenia:** The word "Chronic" was removed from the indication of use. For the Continuation of Therapy criteria, the example of increased platelet counts to denote an example of a beneficial response was moved from an example within the criteria to a Note. Also, maintenance of platelet counts, and/or a decreased frequency of bleeding episodes were also added as examples to the Note as well. **Thrombocytopenia in a Patient with Chronic Hepatitis C:** The provided value as an example of a low platelet count was moved from the criteria to a Note. **Thrombocytopenia in Myelodysplastic Syndrome:** For the Continuation of Therapy criteria, the example of increased platelet counts to denote an example of a beneficial response was moved from an example within the criteria to a Note. Also, maintenance of platelet counts, and/or a decreased frequency of bleeding episodes were also added as examples to the Note as well.	03/17/2021

PRIOR AUTHORIZATION POLICY

POLICY: Thrombocytopenia – Tavalisse Prior Authorization Policy

- Tavalisse® (fostamatinib disodium hexahydrate tablets – Rigel/Patheon Whitby)

REVIEW DATE: 03/17/2021

OVERVIEW

Tavalisse, a tyrosine kinase inhibitor with demonstrated activity against spleen tyrosine kinase, is indicated for the treatment of thrombocytopenia in adults with **chronic immune thrombocytopenia** (ITP) who have had an insufficient response to a previous treatment.[1]

The safety and efficacy of Tavalisse have not been established in pediatric patients. Use of Tavalisse is not recommended for patients < 18 years of age because adverse events on actively growing bones were observed in nonclinical studies. Discontinue Tavalisse if after 12 weeks of treatment the platelet count does not increase to a sufficient level to control bleeding.

Guidelines

In 2019 the American Society of Hematology updated guidelines for ITP.[2] Tavalisse is noted as an agent that has been studied in the third-line setting and its role is not specifically addressed. However, there are several other recommendations. For adults with ITP for at least 3 months who are corticosteroid-dependent or unresponsive to corticosteroid, a thrombopoietin receptor agonist (either Promacta® [eltrombopag tablets and oral suspension] or Nplate® [romiplostim injection for subcutaneous use]) or a splenectomy are recommended. Other treatment options in children and adults include intravenous immunoglobulin, anti-D immunoglobulin, and rituximab.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tavalisse. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tavalisse as well as the monitoring required for adverse events and long-term efficacy, approval requires Tavalisse to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tavalisse is recommended in those who meet the following criteria:

FDA-Approved Indication

~~98.~~95. **Chronic Immune Thrombocytopenia.** Approve if the patient meets one of the following criteria (A or B):

48. Initial Therapy. Approve for 3 months if the patient meets all of the following criteria (i, ii, iii, and iv):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets one of the following (a or b):

- **a)** Patient has a platelet count < 30 x 10^9/L (< 30,000/mcL): OR
- **b)** Patient meets both of the following [(1) and (2)]:
  - **(1)** The patient has a platelet count < 50 x 10^9/L (< 50,000/mcL); AND
  - **(2)** According to the prescriber, the patient is at an increased risk of bleeding; AND

iii. Patient meets one of the following criteria (a or b):

- **a)** Patient has tried at least one other therapy; OR
  Note: Examples of therapies are systemic corticosteroids, intravenous immunoglobulin, anti-D immunoglobulin, Promacta® (eltrombopag tablets and oral suspension), Nplate® (romiplostim injection for subcutaneous use), Doptelet® (avatrombopag tablets), or rituximab.
- **b)** Patient has undergone splenectomy; AND

iv. Medication is prescribed by or in consultation with a hematologist; OR

B. Continuation of Therapy. Approve for 1 year if the patient meets both of the following criteria (i and ii):

iii. According to the prescriber, the patient demonstrates a beneficial clinical response; AND
Note: A beneficial response can include increased platelet counts, maintenance of platelet counts, and/or a decreased frequency of bleeding episodes; AND

iv. Patient remains at risk for bleeding complications.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tavalisse is not recommended in the following situations:

5. B-Cell Lymphomas. Tavalisse has been investigated in patients with various B-cell lymphomas (e.g., non-Hodgkin's lymphoma, diffuse large B-cell lymphoma [DLBCL]).[3,4] Many other therapies are available for this use.

6. Rheumatoid Arthritis. Tavalisse has been studied in patients with rheumatoid arthritis.[5-9] However, other therapies are more well-established and are recommended in guidelines.

7. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes	05/22/2019
Early Annual Revision	**Chronic Immune Thrombocytopenia:** Doptelet was added to the list of alternatives that count towards the criteria that requires a trial of at least one other therapy. Also, the approval duration was changed from 3 years to 1 year.	07/03/2019
Early Annual Revision	**Chronic Immune Thrombocytopenia:** Criteria were divided into Initial Therapy and Continuation of Therapy. For initial therapy, the approval duration is for 3 months. Criteria were added that the patient has a platelet count < 30 x 10^9/L (< 30,000/µL); or that the patient had a platelet count < 50 x 10^9/L (< 50,000/µL) and, according to the	03/11/2020

	prescriber, the patient is at an increased risk of bleeding. Also, regarding the requirement of a trial of at least one therapy, the word "systemic" was added before the word corticosteroids. Continuation of therapy is allowed for a 1 year duration if, according to the prescriber the patient demonstrates a beneficial clinical response (e.g., increase in platelet counts) AND the patient remains at risk for bleeding complications.	
Annual Revision	**Chronic Immune Thrombocytopenia:** For the Continuation of Therapy criteria, the example of increased platelet counts to denote an example of a beneficial response was moved from an example within the criteria to a Note. Also, maintenance of platelet counts, and/or a decreased frequency of bleeding episodes were also added as examples to the Note as well.	03/17/2021

PRIOR AUTHORIZATION POLICY

POLICY: Tolvaptan Products – Jynarque® (tolvaptan tablets – Otsuka)

DATE REVIEWED: 06/10/2020

OVERVIEW

Jynarque, a selective vasopressin V_2-receptor antagonist, is indicated to slow kidney function decline in adults at risk of rapidly-progressing autosomal dominant polycystic kidney disease (ADPKD).[1]

Disease Overview

ADPKD is a heterogeneous, inherited kidney disorder associated with the development of kidney cysts, which result in kidney pain, hypertension, renal failure, and other clinical sequelae.[5-8] The condition is a common cause of end-stage renal disease (ESRD); however, other organs are also impacted (e.g., hepatic and vascular systems). Progressive kidney enlargement occurs; however, manifestations generally do not occur until later in life (fourth decade) due to compensatory renal mechanisms. If a parent has the condition, a child has a 50% chance of inheritance. Approximately 600,000 people in the US have this condition.

Clinical Efficacy

Jynarque was shown to slow the rate of decline in renal function in adults at risk of rapidly-progressing ADPKD in two trials.[1-4] TEMPO 3:4 (n = 1,445) [published] involved adults (18 to 50 years of age) with early, rapidly-progressing (total kidney volume ≥ 750 mL and aged < 51 years) ADPKD who received Jynarque or placebo for up to 3 years.[1-2] Patients had an average estimated glomerular filtration rate (eGFR) of 82 mL/min/1.73 m^2. The prespecified primary endpoint of 3-year change in total kidney volume was achieved with Jynarque therapy ($P < 0.0001$).[1] During the 3-year period, total kidney volume increased by 2.8% per year with Jynarque vs. 5.5% per year with placebo ($P < 0.001$). [2] The difference in total kidney volume occurred mainly in Year 1, with little additional differences noted in Year 2 and 3.[1] The relative rate of ADPKD-related events were decreased by 13.5% in patients randomized to Jynarque compared with placebo (44 vs. 50 events per 100 person-years; $P = 0.0095$). This composite endpoint was primarily driven by decreases in worsening kidney function and kidney pain events.[1-2] TEMPO 4:4 (n = 871) [published] involved patients completing TEMPO 3:4 and provided an additional 2 years of data regarding the effects of Jynarque, as all patients were given active therapy.[1,3] The difference between groups in total kidney volume was not maintained.[1] The percent changes in total kidney volume from the baseline of TEMPO 3:4 to Month 24 of TEMPO 4:4 were 29.9% among those previously receiving Jynarque vs. 31.6% who were given placebo prior [$P = 0.38$]).

REPRISE (n = 1,370) [published] involved adults (18 to 65 years of age) with later stage ADPKD who received Jynarque or placebo for up to 1 year.[1,4] The trial included a prerandomization phase to assess tolerability, as well as a 3-week randomized withdrawal period to evaluate renal function. Patients had an average eGFR of 41 mL/min/1.73 m^2. In the randomized period, the change in eGFR from pretreatment

baseline to post-treatment follow-up was -2.3 mL/min/1.73 m^2/year with Jynarque compared with -3.6 mL/min/1.73 m^2/year with placebo, with a treatment effect of 1.3 mL/min/1.73 m^2/year ($P < 0.0001$). The eGFR slope (with adjustment per trial duration), a key secondary endpoint, also demonstrated a difference between treatment groups of 1.0 mL/min/m^2/year ($P < 0.0001$).

Guidelines

The European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Working Groups on Inherited Kidney Disorders and European Renal Best Practice published a position statement regarding use of tolvaptan in ADPKD (2016).[10] A confirmed eGFR decline ≥ 5 mL/min/1.73 m^2 in 1 year, and/or ≥ 2.5 mL/min/1.73 m^2 per year over a period of 5 years defines rapid progression. Also, a total kidney volume increase > 5% per year by repeated measurements (preferably three or more, each at least 6 months apart and by magnetic resonance imaging) defines rapid progression.[10] The pivotal trials for Jynarque did not involve patients with Stage 5 CKD (glomerular filtration rate [GFR] < 15 mL/min/1.73 m^2 or receiving dialysis).

The National Kidney Foundation and the Polycystic Kidney Disease Foundation, list tolvaptan as an FDA-approved treatment option for patient with ADPKD.[8,11]

Safety

Jynarque has a Boxed Warning regarding a risk of serious liver injury which can be fatal.[1] Monitor transaminases and bilirubin levels prior to therapy initiation, at 2 weeks and 4-weeks after initiation, then continuing monthly for the first 18 months and once every 3 months thereafter.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Jynarque. All approvals are provided for the duration noted below. Due to the specialized skills required for evaluation and diagnosis of patients treated with Jynarque as well as the monitoring required for adverse events and long-term efficacy, approval requires Jynarque to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Jynarque is recommended in those who meet the following criteria:

FDA-Approved Indication

~~99.~~96. **Autosomal Dominant Polycystic Kidney Disease.** Approve for 1 year if the patient meets the following criteria (A, B, C and D):

49. The patient is ≥ 18 years of age; AND

50. The agent is prescribed by or after consultation with a nephrologist; AND

51. According to the prescribing physician, the patient has rapidly-progressing autosomal dominant polycystic kidney disease (e.g., reduced or declining renal function, high or increasing total kidney volume [height adjusted]); AND

52. The patient does not have Stage 5 chronic kidney disease (glomerular filtration rate < 15 mL/min/1.73 m^2 or receiving dialysis).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Jynarque has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below.

8. **Patient is Currently Receiving Samsca® (tolvaptan tablets).** Samsca is a tolvaptan product that is indicated for the treatment of clinically-significant hypervolemic and euvolemic hyponatremia, including patients with heart failure and syndrome of inappropriate antidiuretic hormone.[9] Concomitant use is not recommended.

9. **Hyponatremia.** Samsca is another tolvaptan product indicated for the treatment of clinically-significant hypervolemic and euvolemic hyponatremia (serum sodium < 125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction and fluid restriction), including patients with heart failure and syndrome of inappropriate antidiuretic hormone (SIADH). Samsca should be used for this condition.

10. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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420. Polycystic Kidney Disease Foundation. Tolvaptan. Available at: https://pkdcure.org/tolvaptan/. Accessed on June 3, 2019.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	05/09/2018
Early annual revision	Added the diagnosis of hyponatremia in the Conditions Not Recommended for Approval section.	06/27/2018
Annual review	No change to the criteria.	06/12/2019
Annual Revision	No change to the criteria.	06/10/2020

PRIOR AUTHORIZATION POLICY

POLICY: Tolvaptan Products – Tolvaptan tablets (Samsca® – Otsuka; generics)

DATE REVIEWED: 06/10/2020

OVERVIEW

Samsca, a selective vasopressin V_2-receptor antagonist, is indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium < 125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure (HF) and syndrome of inappropriate antidiuretic hormone (SIADH). Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms should not be treated with Samsca. It has not been established that raising serum sodium with Samsca provides a symptomatic benefit to patients.

Clinical Data

Two trials (Study of Ascending Levels of Tolvaptan in Hyponatremia 1 and 2 [SALT-1 and SALT-2; n = 424]) demonstrated that Samsca increased serum sodium effectively in patients with euvolemic or hypervolemic hyponatremia that was due to many underlying causes (e.g., HF, liver cirrhosis, SIADH).[1,2] Patients (aged ≥ 18 years) received therapy for 30 days with Samsca or placebo and were followed for an additional 7 days after study withdrawal. Patients in the trial had a serum sodium < 135 mEq/L at study entry (baseline 129 mEq/L). In both trials, Samsca therapy led to a greater increase in serum sodium ($P < 0.0001$) compared with baseline for the measured endpoints at Day 4 and Day 30. The effects of sustained serum sodium were demonstrated for up to 1 year in an open-label study.[1] Another long-term analysis (the Safety and sodium Assessment of Long-term Tolvaptan With hyponatremia: A year-long, open-label Trial to gain Experience under Real-world conditions [SALTWATER]) showed that in 111 patients who received Samsca for approximately 1 year, increases in serum sodium were maintained.[1,3]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Samsca. All approvals are provided for up to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Samsca is recommended in those who meet the following criteria:

FDA-Approved Indications

52. Hyponatremia. Approve for up to 30 days if patient meets ONE of the following criteria (A, B, or C):

- **A)** The patient has a serum sodium < 125 mEq/L at baseline; OR
- **B)** The patient meets the following criteria (i and ii):
  - **i.** The patient has less marked hyponatremia, defined as serum sodium < 135 mEq/L at baseline; AND
  - **ii.** The patient has symptomatic hyponatremia.
    Note: Symptoms of hyponatremia include nausea, vomiting, headache, lethargy, confusion; OR
- **C)** The patient has already been started on Samsca and has received < 30 days of therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Samsca has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

11. **Autosomal Dominant Polycystic Kidney Disease (ADPKD).** Jynarque (tolvaptan tablets) is another tolvaptan product that is indicated to slow kidney function decline in adults at risk of rapidly-progressing ADPKD. The recommended dosing differs.[4] The Samsca prescribing information states that tolvaptan should not be prescribed or used to treat ADPKD outside of the FDA-approved REMS for ADPKD.

12. **Patient is Currently Receiving Jynarque® (tolvaptan tablets).** Jynarque is another tolvaptan product that is indicated to slow kidney function decline in adults at risk of rapidly-progressing ADPKD. Concomitant use is not recommended.

13. **Patients Requiring Intervention to Raise Serum Sodium Urgently to Prevent or to Treat Serious Neurological Symptoms.** Samsca has not been studied in a setting of urgent need to raise serum sodium acutely.[1]

14. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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580. Jynarque™ tablets for oral use [prescribing information]. Rockville, MD: Otsuka Pharmaceuticals; January 2020.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual revision	No criteria changes	06/28/2017
Annual revision	Added autosomal dominant polycystic kidney disease and concomitant Jynarque use in the Conditions Not Recommended for Approval section.	06/27/2018
Annual revision	No criteria changes.	06/12/2019
Annual Revision	No criteria changes.	06/10/2020

PRIOR AUTHORIZATION POLICY

POLICY: Topical Acne – Winlevi Prior Authorization Policy

- Winlevi® (clascoterone cream 1% – Cassiopea Inc)

REVIEW DATE: 12/16/2020

OVERVIEW

Winlevi, an androgen receptor inhibitor, is indicated for the **topical treatment of acne vulgaris** in patients ≥ 12 years of age.[1]

Safety

Winlevi is the only topical acne product with a warning about hypothalamic-pituitary-adrenal (HPA) axis suppression.[1] This may result when Winlevi is used over large surface areas or if use is prolonged. In addition, pediatric patients may be more susceptible. This adverse event was not observed in the pivotal studies or in the long-term open-label extension study. However, it was observed in a small group of patients on Day 14 in a pharmacokinetic study. Normal HPA axis function was observed at follow-up at 4 weeks after end of treatment.

Guidelines

Winlevi has not been added to the American Academy of Dermatology guidelines for the management of acne (2016).[2] Topical therapies, either as monotherapy, or in combination with other topical agents or oral agents are recommended for initial control and maintenance therapy of acne. Topical retinoids are the cornerstone of acne management due to their comedolytic and anti-inflammatory properties.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Winlevi. All approvals are provided for the duration noted below.

Automation: None

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Winlevi is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Acne Vulgaris.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **53.** Patient is ≥ 12 years of age; AND
   - **54.** Patient has tried at least one prescription topical retinoid.
     Note: Examples of a prescription topical retinoid are adapalene, Aklief® [trifarotene cream 0.005%], tazarotene (Tazorac® 0.1% cream [generics], Tazorac 0.1% gel), and tretinoin; AND
   - **55.** Patient has tried at least three other prescription topical therapies.
     Note: Examples of other prescription topical therapies for acne include: Aczone® (dapsone gel 7.5%; dapsone gel 5% [generics]), Azelex® (azelaic acid cream 20%), topical clindamycin, topical erythromycin, and topical minocycline (Amzeeq™ [minocycline foam 4%]).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Winlevi is not recommended in the following situations:

- **15.** Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Winlevi® cream [prescribing information]. San Diego, CA: Cassiopea Inc; August 2020.
2. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2016;74:945-73.

HISTORY

Type of Revision	Summary of Changes	Review Date
New policy	--	12/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Topical Acyclovir Cream and Ointment Prior Authorization Policy
- Zovirax® (acyclovir 5% cream – Valeant, generics)
- Zovirax® (acyclovir 5% ointment – Valeant, generics)

REVIEW DATE: 06/24/2020

OVERVIEW

Acyclovir 5% cream (Zovirax, generics) is indicated for the treatment of recurrent herpes labialis (cold sores) in immunocompetent adults and adolescents 12 years of age and older.[1] Acyclovir 5% ointment (Zovirax, generics) is indicated in the management of initial genital herpes and in limited non-life-threatening mucocutaneous herpes simplex virus infections in immunocompromised patients.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of acyclovir 5% cream and acyclovir 5% ointment. All approvals are provided for the duration noted below. For the ointment, a trial of generic acyclovir 5% ointment is required prior to approval of brand Zovirax 5% ointment.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of acyclovir 5% cream (Zovirax 5% cream, generics) is recommended in those who meet the following criterion:

FDA-Approved Indication

28. Herpes Labialis (Cold Sores). Approve for 1 year if the patient meets both of the following criteria (A and B):
- **a)** Patient is ≥ 12 years of age; AND
- **b)** Patient is immunocompetent.

II. Coverage of acyclovir 5% ointment (Zovirax 5% ointment, generics) is recommended in those who meet the following criteria:

FDA-Approved Indications

29. Genital Herpes. Approve for 1 year if the patient meets one of the following criteria (A or B):
- a. Generic acyclovir 5% ointment is requested; OR
- b. If brand Zovirax 5% ointment is requested, the patient meets both of the following criteria (i and ii):
  - i. Patient has tried generic acyclovir 5% ointment; AND
  - ii. Patient cannot use the generic product to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic

product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

30. Limited Non-Life-Threatening Mucocutaneous Herpes Simplex Virus Infections. Approve for 1 year if the patient meets one of the following criteria (A and B):
   a. Patient is immunocompromised; AND
   b. Patient meets one of the following criteria (i or ii):
      i. Generic acyclovir 5% ointment is requested; OR
      ii. If brand Zovirax 5% ointment is request, the patient meets both of the following criteria (a and b):
         1. Patient has tried generic acyclovir 5% ointment; AND
         2. Patient cannot use the generic product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of acyclovir 5% cream and acyclovir 5% ointment are not recommended in the following situation:

13. Shingles. Shingles is a viral infection caused by the varicella-zoster virus, the same virus that causes chickenpox.[3,4] The Centers for Disease Control and Prevention (CDC) and the National Institute of Health (NIH), National Institute of Neurological Disorders and Stroke (NINDS) cite the use of oral antivirals (acyclovir capsules/tablets/suspension [Zovirax, generics], famciclovir tablets [Famvir®, generics], and valacyclovir caplets [Valtrex®, generics]) for the treatment of shingles. Oral antivirals speed healing and reduce the risk of complications. Topical antivirals are not noted as treatment options for shingles.

14. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

116. Zovirax® cream [prescribing information]. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC; January 2017.
117. Zovirax® ointment [prescribing information]. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC; January 2017.
118. Centers for Disease Control and Prevention – Shingles. Available at: http://www.cdc.gov/shingles/about/prevention-treatment.html. Updated July 2019. Accessed on June 12, 2020.
119. National Institute of Health, National Institute of Neurological Disorders and Stroke – Shingles: Hope through research. Available at: https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Hope-Through-Research/Shingles-Hope-Through-Research#3223_8. Updated March 2020. Accessed on June 12, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes	06/13/2018
Update	03/08/2019: Addition of generic acyclovir cream to the policy; no criteria changes	--
Annual revision	For Zovirax ointment: current criterion asks about the use of generic acyclovir ointment. The standard language regarding brand/generic is added.	06/12/2019
Annual revision	Policy name revised from "Zovirax (Topical) PA Policy" to "Topical Acyclovir Cream and Ointment PA Policy. No criteria changes.	06/24/2020

POLICY: Topical Alpha-Adrenergic Agonists for Rosacea
- Mirvaso® (brimonidine gel, 0.33% – Galderma)
- Rhofade™ (oxymetazoline hydrochloride cream, 1% – EPI Health)

DATE REVIEWED: 05/27/2020

OVERVIEW

The topical alpha-adrenergic agonists, Mirvaso and Rhofade, are indicated for the topical treatment of persistent facial erythema associated with rosacea in adults ≥ 18 years of age.[1,2]

Mirvaso is an alpha$_2$-adrenergic agonist and Rhofade is an alpha$_{1A}$-adrenergic agonist. Both of these products have been shown to decrease the erythema associated with rosacea; neither has been shown to exert any beneficial effects on inflammatory lesions.[1-4]

Rosacea, a chronic, inflammatory facial skin disorder, affects approximately 16 million people in the US.[5-7] The hallmark of rosacea is centrofacial persistent erythema, typically affecting the cheeks, chin, forehead, and nose; the perioral and periocular regions are generally unaffected.[6] Patients with rosacea typically present with clinical manifestations that include flushing, persistent facial erythema, dryness, burning and stinging skin, inflammatory papules and pustules, telangiectasia or dilation of blood vessels, and watery or irritated eyes.[7] Diffuse centrofacial erythema is almost universally present in all patients with rosacea; it generally intensifies in magnitude during a flare and persists between flares at a lesser degree of intensity.[8]

The American Acne & Rosacea Society (AARS) published consensus guidelines on the management of rosacea in 2014.[3,4] The panel notes that a gentle skin care and photoprotection regimen is recommended for all patients. A topical alpha-adrenergic agonist is recommended for use as monotherapy in patients with centrofacial erythema without papulopustular lesions or in combination with an anti-inflammatory (e.g., topical metronidazole, azelaic acid 15% gel [Finacea®, generics], Finacea® foam [azelaic acid], ivermectin 1% cream [Soolantra®, generics]) in patients with centrofacial erythema and papulopustular lesions. The topical alpha-agonists should not be considered as alternatives to anti-inflammatory therapies.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of the topical alpha-adrenergic agonists. All approvals are provided for 1 year in duration.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Mirvaso or Rhofade is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Facial Erythema Due to Rosacea in Adults ≥ 18 years of age.** Approve for 1 year.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Neither Mirvaso nor Rhofade has been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

16. Erythema Caused by Conditions Other Than Rosacea.

17. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual Revision	No criteria changes	05/30/2018
Annual Revision	No criteria changes	05/29/2019
Annual Revision	No criteria changes	05/27/2020

PRIOR AUTHORIZATION POLICY

POLICY: Topical Diclofenac Sodium Gel (Solaraze) Prior Authorization Policy

- Solaraze® (diclofenac sodium 3% gel – PharmaDerm, generics)

REVIEW DATE: 06/24/2020

OVERVIEW

Diclofenac sodium 3% gel (Solaraze®, generics) is a topical nonsteroidal anti-inflammatory drug (NSAID) indicated for the topical treatment of actinic keratoses (AK).[1] It is also noted in the labeling that sun avoidance is indicated during therapy. The mechanism of action of diclofenac sodium in the treatment of AK is unknown or not completely understood; however, it is hypothesized that diclofenac sodium may clear AK lesions via cell signaling mechanisms and possibly may play a part in the reduction of angiogenesis and induction of apoptosis (either directly or through a cytotoxic independent pathway).[2]

There are other topical NSAIDs commercially available in the US: diclofenac sodium topical 1% gel (Voltaren® Gel, generics) which is indicated for the relief of the pain of osteoarthritis (OA) of joints amenable to topical treatment, such as the knees and those of the hands; Flector® Patch (diclofenac epolamine 1.3% topical patch) which is indicated for the topical treatment of acute pain due to minor strains, sprains, and contusions; and Pennsaid® (diclofenac sodium 2% w/w topical solution) which is indicated for the treatment of the pain of OA of the knee(s).[3-5]

Other Uses

There are data to support the use of diclofenac sodium 3% gel for the treatment of actinic cheilitis (actinic keratosis of the lips). In a study where 31 patients with actinic cheilitis were treated with diclofenac 3% gel for a period of 90 days, ten patients showed total remission and three patients showed partial improvement.[6] A report of six cases treated with diclofenac sodium 3% gel demonstrated complete response for five patients and partial response for one patient, after 6 weeks of treatment.[7] In an open-label study involving 27 patients with actinic cheilitis who completed 30 to 180 days of therapy with diclofenac 3% in 2.5% hyaluronic acid gel, complete remission was observed in 44% of patients (n = 12/27) and a significant improvement in 56% (n = 15/27) of patients was observed.[8] Another open-label study demonstrated efficacy with diclofenac sodium 3% gel when used for 90 days in 19 patients with actinic cheilitis.[9]

Diclofenac can also be used for the treatment of Bowen's disease, a form of squamous cell carcinoma in situ.[10,11] There are two published case series (one involving two patients, another involving five patients) which demonstrated clinical and histological resolution of Bowen's disease in all seven patients. In one case series, patients were treated for 90 days, while in the other case series, patients were treated for 8 weeks. Available guidelines detailing management of Bowen's disease note that evaluation of studies on the treatment of Bowen's disease can be problematic due to the varying healing and success rates with the varying locations of the lesions/patches.[12,13] In addition, the management of Bowen's disease employs several different types of treatment and, like the management of AK, selection of therapy depends on various factors such as lesion characteristics, lesion location, etc. The main treatment options used for Bowen's disease include topical fluorouracil (5-FU), imiquimod, cryotherapy, curettage, excision, photodynamic therapy, radiotherapy, and laser.[12]

The use of diclofenac sodium 3% gel has been studied in a small open-label study (exact formulation not specified) and in one case series for the management of patients with disseminated superficial actinic porokeratosis (DSAP).[14,15] In the open-label study, 17 adults with DSAP initially received 12 weeks of therapy with diclofenac sodium 3% gel and could continue for an additional 12 weeks.[14] At 12 weeks, the target area lesions (treated lesions) had a mean reduction of 4% vs. a 12% mean increase in the total body (global) lesions. For those ten patients who received 24 weeks of therapy, there was a mean increase in the target area lesions of 10% vs. a mean increase of 19% for the total body (global) lesions at that time point. Only three of the ten patients who completed 24 weeks of therapy had a reduction in their number of lesions. In the eight patient case series, all patients received diclofenac sodium 3% gel for at least 6 months.[15] All of these DSAP patients had tried at least one other therapy (mean was three previous therapies) prior to diclofenac sodium 3% gel. Only two of the eight patients (25%) had a partial response at 6 months. Three other patients received more than 6 months of treatment (7 or 13 months), but none experienced a response. As is typical of other therapies tried for the management of DSAP, results with diclofenac sodium 3% gel demonstrated limited, if not marginal, effectiveness. Most of the therapies tried for DSAP (e.g., cryotherapy, topical 5-FU, topical vitamin D_3 analogs, retinoids, keratolytics, imiquimod, laser, and photodynamic therapy) are ineffective.[14-16]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of diclofenac sodium 3% gel. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of diclofenac sodium 3% gel is recommended in those who meet the following criteria:

FDA-Approved Indications

56. Actinic Keratoses. Approve for 6 months.

Other Uses with Supportive Evidence

57. Actinic Cheilitis (Actinic Keratoses of the Lip[s]). Approve for 6 months.

3. Bowen's Disease. Approve for 6 months after a trial of at least one other therapy used for the management of Bowen's disease.
Note: Examples of therapies for Bowen's disease include: topical 5-fluorouracil [5-FU], imiquimod, cryotherapy, photodynamic therapy, curettage, excision, laser, or radiotherapy.

4. Disseminated Superficial Actinic Porokeratosis. Approve for 6 months after a trial of at least two other therapies used for the management of disseminated superficial actinic porokeratosis.
Note: Examples of therapies for management of disseminated superficial actinic porokeratosis: topical 5-fluorouracil [5-FU], imiquimod, topical corticosteroids, topical vitamin D_3 analogs, topical or oral retinoids, cryotherapy, photodynamic therapy, and laser.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of diclofenac sodium 3% gel is not recommended in the following situations:

18. Osteoarthritis (OA). The benefit of topical diclofenac therapy in osteoarthritis is uncertain. There has been one small, randomized, placebo-controlled study assessing the efficacy of a topical diclofenac 3%/sodium hyaluronate 2.5% gel (Canadian formulation) applied as 2 grams four times daily to one joint for 2 weeks in patients (n = 119) with uncontrolled OA pain despite chronic (≥ 1 month) oral nonsteroidal anti-inflammatory drug (NSAID) use.[17] The addition of topical diclofenac 3%/sodium hyaluronate to oral NSAID therapy resulted in only marginally greater analgesic effect than NSAID alone. Other topical agents are indicated for this use.

19. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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591. Voltaren® Gel [prescribing information]. Malvern, PA: Endo Pharmaceuticals, Inc; February 2018.
592. Flector® Patch [prescribing information]. New York, NY: Pfizer; August 2018.
593. Pennsaid® topical solution [prescribing information]. Lake Forest, IL: Horizon Pharma; May 2016.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	06/13/2018
Annual Revision	No criteria changes.	06/12/2019
Update	Policy name revised from Solaraze PA to Diclofenac sodium gel (Solaraze) PA.	03/13/2020
Update	Policy name revised from Diclofenac sodium gel (Solaraze) PA to Topical Diclofenac Sodium Gel (Solaraze) PA.	03/30/2020
Annual Revision	Examples of therapies for management of Bowen's Disease and Disseminated Superficial Actinic Porokeratosiss are changed to Notes. No criteria changes.	06/24/2020

PRIOR AUTHORIZATION POLICY

POLICY: Topical Retinoids – Aklief Prior Authorization Policy

- Aklief® (trifarotene cream – Galderma Laboratories)

REVIEW DATE: 12/02/2020

OVERVIEW

Aklief, a topical retinoid, is indicated for the **topical treatment of acne vulgaris** in patients 9 years of age and older.

Aklief has not been added to the guidelines. Topical retinoids are effective for the treatment of acne, both as initial and maintenance therapy. Treatment algorithms and consensus statements do not differentiate between the topical retinoids, but rather refer to them as a therapeutic category.[2-5]

Topical retinoid products (e.g., tretinoin) have been used to treat numerous other medical skin conditions in addition to acne vulgaris.[6] Some indications have minimal published clinical data and thus appear experimental. Topical retinoid products have also been used to treat a variety of cosmetic skin conditions, such as wrinkles, stretch marks, liver spots, premature aging, and photo-aged or photo-damaged skin.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Aklief. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indication

58. Acne Vulgaris. Approve for 3 years.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Aklief is not recommended in the following situations:

20. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

References

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	12/04/2019
Annual Revision	No criteria changes.	12/02/2020

PRIOR AUTHORIZATION POLICY

POLICY: Topical Retinoids – Panretin Prior Authorization Policy

- Panretin® (alitretinoin topical gel – Eisai, Inc.)

REVIEW DATE: 06/24/2020

OVERVIEW

Panretin, a topical retinoid, is indicated for topical treatment of cutaneous lesions in patients with Acquired Immunodeficiency Syndrome (AIDS)-related Kaposi sarcoma (KS).[1] It is not indicated when systemic anti-KS therapy is required (e.g., more than 10 new KS lesions in the prior month, symptomatic lymphedema, symptomatic pulmonary KS, or symptomatic visceral involvement). There is no experience to date using Panretin gel with systemic anti-KS treatment.

Disease Overview

KS is a multifocal malignancy of endothelial cells, presenting with characteristic red or brown papules.[2,3] Skin lesions are most common although other areas may be involved, including the oral mucosa and lymphatic system.[4] KS is caused by human herpesvirus 8, which is also known as KS-associated herpesvirus (KSHV).[2] KSHV infections are usually asymptomatic but may lead to disease in immunosuppressed individuals. The incidence of KS in the US is approximately six cases per million people annually.[3] AIDS-related KS, also known as epidemic KS, is the most common type of KS in the United States. In persons infected with HIV, the development of KS is an AIDS-defining illness. Additionally, about one in 200 transplant recipients in the US will develop KS (iatrogenic/transplant-associated KS). In the iatrogenic/transplant-associated form, adequate response is often achieved by reduction or cessation of immunosuppression. Other forms of KS include classic KS and endemic KS, which are not common in the US.

Guidelines

Use of Panretin is addressed in the National Comprehensive Cancer Network (NCCN) guidelines for AIDS-related KS (version 2.2020 – June 1, 2020).[2] For limited cutaneous AIDS-releated KS that is symptomatic and/or cosmetically unacceptable, antiretroviral therapy may be used with or without topical agents (i.e.,

Panretin or imiquimod 5% cream), systemic therapy, intralesional chemotherapy, radiation therapy, or local excision (all category 2A). For patients with advanced cutaneous, oral, visceral, or nodal disease, Panretin is not recommended; a clinical trial, systemic therapy, or radiation treatment may be used (all in conjunction with antiretroviral therapy).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Panretin. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Panretin, approval requires Panretin to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Prior authorization and prescription benefit coverage are not recommended for cosmetic uses.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Panretin is recommended in those who meet the following criteria:

FDA-Approved Indications

29. Kaposi Sarcoma Related to Acquired Immunodeficiency Syndrome. Approve for 1 year if the patient meets all of the following (A and B):
Note: Kaposi sarcoma related to Acquired Immunodeficiency Syndrome may also be referred to as epidemic Kaposi sarcoma.

H) Patient is not receiving systemic therapy for Kaposi sarcoma; AND

I) Panretin is prescribed by or in consultation with a dermatologist, oncologist, or infectious disease specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Panretin is not recommended in the following situations:

7. Cosmetic Uses (e.g., photoaging of the skin). Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical pharmacy benefit.

8. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	06/12/2019
Annual Revision	No changes to criteria.	06/24/2020

PRIOR AUTHORIZATION POLICY

POLICY: Topical Retinoids – Tazarotene Products Prior Authorization Policy

- Arazlo™ (tazarotene 0.045% lotion – Bausch Health US, LLC)
- Fabior® (tazarotene 0.1% foam – Mayne Pharma)
- Tazorac® (tazarotene 0.05% cream, 0.05% gel and 0.1% cream [generics], 0.1% gel – Allergan)

REVIEW DATE: 07/01/2020

OVERVIEW

Tazorac gel is indicated for the following uses:[1]

- **Plaque psoriasis**, in patients with up to 20% body surface area involvement (0.05% and 0.1% strengths)
- **Facial acne vulgaris,** in patients with mild to moderate severity (0.1% strength only).

Tazorac cream (0.05% and 0.1%) is indicated for the following uses:[2]

- **Plaque psoriasis** involvement (0.05% and 0.1% strengths).
- **Acne vulgaris** (0.1% strength only).

Arazlo lotion is indicated for the topical treatment of acne vulgaris in patients ≥ 9 years of age.[3]

Fabior foam is indicated for the topical treatment of acne vulgaris use in patients ≥ 12 years of age.[4]

In addition to acne vulgaris and plaque psoriasis, topical tazarotene has been used to treat other medical skin conditions, such as basal cell carcinoma and congenital ichthyoses.[5] Topical tazarotene has also been used to treat cosmetic skin conditions such as wrinkles, premature aging, and treatment of photo-aged or photo-damaged skin.

Avage® (tazarotene 0.1% cream) is indicated as an adjunctive agent for the mitigation (palliation) of facial fine wrinkling, facial mottled hyper- and hypo-pigmentation, and benign facial lentigines in patients who use comprehensive skin care and sunlight avoidance programs.[6] Avage is not included in this Prior Authorization policy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Arazlo, Fabior, and Tazorac. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of topical tazarotene products is recommended for those who meet the following criteria:

FDA-Approved Indications

1. **Acne Vulgaris.** Approve for 3 years.

2. **Plaque Psoriasis (Psoriasis Vulgaris).** Approve for 3 years.

Other Uses with Supportive Evidence

3. **Treatment of Other Non-Cosmetic Conditions Not Listed Above.** Approve for 1 year.
   Note: Examples of other non-cosmetic conditions include: psoriasis of fingernails or toenails, oral lichen planus, congenital ichthyoses (X-linked recessive ichthyosis, non-erythrodermic autosomal recessive lamellar ichthyosis, autosomal dominant ichthyosis vulgaris), basal cell carcinoma, mycosis fungoides, cutaneous T-cell lymphoma, keratosis pilaris (atrophicans), actinic keratoses, skin neoplasms, warts, dermatitis/eczema, folliculitis, acne rosacea, cystic acne, comedonal acne.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of topical tazarotene products is not recommended in the following situations:

1. **Cosmetic Conditions.** Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical pharmacy benefit.
   Note: Examples of cosmetic conditions include: alopecia, hyperpigmentation, liver spots, melasma/cholasma, seborrheic keratosis, stretch marks, scarring, wrinkles, premature aging, photo-aged or photo-damaged skin, mottled hyper- and hypopigmentation, benign facial lentigines, roughness, telangiectasia, skin laxity, keratinocytic atypia, melanocytic atypia, dermal elastosis.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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3. Arazlo™ lotion [prescribing information]. Bridgewater, NJ: Bausch Health US, LLC; December 2019.
4. Fabior foam 0.1% [prescribing information]. Greenville, NC: Mayne Pharma; November 2016.
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6. Avage cream 0.1% [prescribing information]. Irvine, CA: Allergan, Inc.; September 2016.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	No criteria changes.	07/18/2018
Annual revision	No criteria changes.	07/31/2019
Update	Changed policy name from "Tazarotene (Topical) Products PA Policy" to "Topical Retinoids – Tazarotene Products PA Policy".	11/21/2019
Selected revision	• Addition of Arazlo (tazarotene 0.045% lotion) to the PA Policy. • **Acne vulgaris.** The list of examples of topical retinoid products was removed from the criteria and changed to a note. In addition, Aklief was added to the list of examples of topical retinoid products.	01/29/2020
Annual revision	• **Acne Vulgaris.** Removed the requirement that patient has had a trial with at least one other topical retinoid product. • The lists of examples of "other non-cosmetic conditions" and "cosmetic conditions" were removed from the criteria and changed to a note.	07/01/2020

PRIOR AUTHORIZATION POLICY

POLICY: Topical Retinoid – Tretinoin Products Prior Authorization Policy

- Altreno™ (tretinoin lotion – Dow Pharmaceuticals, a division of Valeant Pharmaceuticals)
- Atralin™ (tretinoin gel – Valeant Pharmaceuticals, generics)
- Avita® (tretinoin cream, gel – Mylan, generics [Avita gel 0.025% is brand only])
- Retin-A® (tretinoin cream, gel – Valeant Pharmaceuticals, generics)
- Retin-A® Micro® (tretinoin gel microsphere – Valeant Pharmaceuticals, generic)
- Retin-A Micro® Pump (tretinoin gel microsphere – Valeant Pharmaceuticals, generics [Retin-A Micro gel 0.06% and 0.08% are branded products only])
- Tretin•X® (tretinoin cream – Onset Dermatologicals)
- Veltin™ (clindamycin phosphate 1.2% and tretinoin 0.025% gel – Aqua Pharmaceuticals)
- Ziana® (clindamycin phosphate 1.2% and tretinoin 0.025% gel – Valeant Pharmaceuticals, generics)

REVIEW DATE: 08/05/2020

OVERVIEW

The following topical tretinoin products are indicated for the topical treatment of acne vulgaris: Altreno, Atralin, Avita, Retin-A, Retin-A Micro, Tretin•X, and generics.[1,2] Renova® and Refissa® are also topical tretinoin products; these products are not indicated for use in the treatment of acne vulgaris.[1]

Ziana and Veltin are combination gel products containing clindamycin phosphate 1.2% and tretinoin 0.025%; these products are indicated for the topical treatment of acne vulgaris in patients aged ≥ 12 years.[1,2]

Topical tretinoin products have been used to treat numerous other medical skin conditions in addition to acne vulgaris. Some indications have minimal published clinical data and thus appear experimental. Topical tretinoin products have also been used to treat a variety of cosmetic skin conditions, such as wrinkles, stretch marks, liver spots, premature aging, and photo-aged or photo-damaged skin.[2]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of topical tretinoin products. All approvals are provided for the duration noted below.

Prior Authorization and prescription benefit coverage is not recommended for Renova or Refissa.

Automation: An age edit targeting patients > 30 years of age is recommended to monitor for appropriate use and to screen for cosmetic use. Therefore, patients ≤ 30 years of age will be approved at the point-of-service. For patients > 30 years of age, coverage will be determined by the prior authorization criteria.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of topical tretinoin products is recommended in those who meet the following criteria:

FDA-Approved Indication

59. Acne Vulgaris. Approve for 3 years.

Other Uses with Supportive Evidence

~~**60.**~~ **Treatment of Other Non-Cosmetic Conditions Not Listed Above**. Approve for 1 year.
Note: Examples of other non-cosmetic conditions include acne rosacea, actinic keratosis/treatment of precancerous lesions, ichthyosis, diabetic foot ulcers, mucositis, warts, lichen planus, lichen sclerosis, pseudofolliculitis, oral leukoplakia, molluscum contagiosum, Darier's disease (keratosis follicularis), dermatitis/eczema, folliculitis, keratosis pilaris, basal cell carcinoma (skin cancer), confluent and reticulated papillomatosis, and cutis laxa.

II. Coverage of clindamycin plus tretinoin combination products (Ziana, generics; Veltin) is recommended in those who meet the following criteria:

FDA-Approved Indication

1. Acne Vulgaris. Approve for 1 year.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of topical tretinoin products and topical clindamycin/tretinoin products is not recommended in the following situations:

21. Cosmetic Conditions. Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical pharmacy benefit.
Note: Examples of cosmetic conditions include liver spots, stretch marks, scarring, solar elastosis, premature aging, treatment of photo-aged or photo-damaged skin, solar lentigines, skin roughness, mottled hyperpigmentation, age spots, wrinkles, geographic tongue, hyperpigmentation (caused by folliculitis, acne, or eczema), melasma/cholasma, alopecia androgenetic, alopecia areata, seborrheic keratosis, milia, nevus, poikiloderma (of Civatte), purpura (actinic/solar), keloids, and sebaceous hyperplasia.

22. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

30. Facts and Comparisons® Online. Wolters Kluwer Health, Inc.; 2020. Available at: http://online.factsandcomparisons.com/login.aspx?url=/index.aspx&qs=. Accessed on July 29, 2020. Search term: tretinoin.
31. DRUGDEX® System. Thomson Reuters (Healthcare) Inc. Available at: http://www.micromedexsolutions.com/micromedex2/librarian/. Accessed on July 29, 2020. Search term: tretinoin..

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	No criteria changes.	07/18/2018
Selected revision	Addition of Altreno (tretinoin lotion).	09/19/2018
Annual revision	No criteria changes.	07/31/2019
Update	11/21/2019: Change policy name from "Tretinoin (Topical) Products PA Policy" to "Topical Retinoids – Tretinoin Products PA Policy".	NA
Annual revision	No criteria changes.	08/05/2020

NA – Not applicable.

PRIOR AUTHORIZATION POLICY

POLICY: Uplizna Prior Authorization Policy

- Uplizna™ (inebilizumab-cdon injection for intravenous use – Viela Bio)

REVIEW DATE: 06/24/2020; selected revision 09/16/2020

OVERVIEW

Uplizna, a CD19-directed cytolytic antibody, is indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in patients ≥ 18 years of age who are anti-aquaporin-4 antibody positive.[1] The recommended dose is 300 mg administered as an intravenous infusion under the close supervision of an experienced healthcare professional. The initial infusion is followed 2 weeks later by a second infusion. Starting 6 months from the first infusion, subsequent doses are administered once every 6 months.

Disease Overview

NMOSD is a rare, relapsing, autoimmune disorder of the brain and spinal cord with optic neuritis and/or myelitis as predominate characteristic symptoms.[2] NMOSD often causes significant, permanent damage to vision and/or spinal cord function causing blindness or impaired mobility.[3] Patients may experience pain, paralysis, loss of bowel and bladder control, loss of visual acuity, uncontrolled motor functions, and complications can cause death. Soliris® (eculizumab injection for intravenous infusion) and Enspryng™ (satralizumab-mwge for subcutaneous injection) are two other FDA-approved medications for treatment of NMOSD in adults who are anti-AQP4 antibody-positive.[4,5] For acute attacks, typical treatment is high-dose intravenous corticosteroids.[6,7] Plasma exchange may be effective in patients who suffer acute severe attacks that do not response to intravenous corticosteroids. For long-term control of the disease a variety of immunosuppressive drugs are utilized as first-line therapy. While all are considered off-label use, corticosteroids, azathioprine, mycophenolate mofetil, and rituximab are treatments prescribed as preventative therapy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Uplizna. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Uplizna as well as the monitoring required for adverse events and long-term efficacy, approval requires Uplizna to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Uplizna is recommended in those who meet the following criteria:

FDA-Approved Indications

~~100.~~97. **Neuromyelitis Optica Spectrum Disorder**. Approve if the patient meets ONE of the following criteria (A or B):

E) Initial Therapy. Approve for 1 year if the patient meets the following criteria (i, ii, iii, iv, and v):

xi. Patient is ≥ 18 years of age; AND

xii. Neuromyelitis optica spectrum disorder diagnosis was confirmed by blood serum test for anti-aquaporin-4 antibody positive; AND

xiii. Patient is currently receiving or has previously tried two of the following systemic therapies (a, b, c, or d):

a. Azathioprine; OR

b. Corticosteroid; OR

c. Mycophenolate mofetil; OR

d. Rituximab; AND

Note: An exception to the requirement for a trial of a systemic therapy can be made if the patient has already tried Soliris® (eculizumab injection) or Enspryng™ (satralizumab-mwge for subcutaneous injection) for neuromyelitis optica spectrum disorder. Patients who have already tried Soliris or Enspryng for neuromyelitis optica spectrum disorder are not required to try another systemic agent for neuromyelitis optica spectrum disorder.

xiv. Patient has a history of at least 1 relapse in the last 12 months or two relapses in the last 2 years; AND

xv. The medication is being prescribed by or in consultation with a neurologist.

F) Patients Currently Receiving Uplizna. Approve for 1 year if the patient meets the following (i, ii, iii, and iv):

ix. Patient is ≥ 18 years of age; AND

x. Neuromyelitis optica spectrum disorder diagnosis was confirmed by blood serum test for anti-aquaporin-4 antibody positive; AND

xi. According to the prescriber, patient has had clinical benefit from the use of Uplizna; AND

Note: Examples of clinical benefit include reduction in relapse rate, reduction in symptoms (e.g., pain, fatigue, motor function), and a slowing progression in symptoms.

xii. The medication is being prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Uplizna is not recommended in the following situations:

270. Concomitant use with a rituximab product, Soliris® (eculizumab injection), or Enspryng™ (satralizumab-mwge injection). There is no evidence to support additive efficacy of combining Uplizna with rituximab, Soliris, or Enspryng.

271. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

826. Uplizna™ injection [prescribing information]. Gaithersburg, MD: Viela Bio, Inc; June 2020.
827. National Organization for Rare Disorders. Neuromyelitis Optica Spectrum Disorder. Available at: https://rarediseases.org/rare-diseases/neuromyelitis-optica/. Accessed June 16, 2020.
828. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015;85(2):177-189.
829. Enspryng™ injection [prescribing information]. South San Fransico, CA: Genentech; August 2020.
830. Soliris® injection [prescribing information]. Boston, MA: Alexion Pharmaceuticals; June 2019.
831. Bradshaw M and Kimbrough D. Neuromyelitis Optica Spectrum Disorders. *Practical Neurology*. 2019;76-84.
832. Siegel Rare Neuroimmune Association. Neuromyelitis Optica Spectrum Disorders. https://wearesrna.org/wp-content/uploads/2018/06/About_NMOSD_2018.pdf. Accessed June 19, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	06/24/2020
Selected Revision	**Neuromyelitis Optica Spectrum Disorder.** Criteria was separated into Initial Therapy and Patients Currently Receiving Uplizna. For both sections, criteria for approval duration, age restriction, diagnosis confirmation, and specialist requirement remained the same as before. For Initial Therapy, Soliris was removed as an option for previously tried systemic therapies. A Note was created to allow an exception to previously tried systemic therapies for patients who have tried Enspryng or Soliris. Criteria for a history of previous relapses were added. For Patients Currently Receiving Uplizna, criteria was added to show the patient is receiving a clinical benefit from Uplizna. **Concomitant use with a rituximab product, Soliris® (eculizumab injection), or Enspryng™ (satralizumab-mwge injection)** was added as a condition not recommended for approval.	09/16/2020

PRIOR AUTHORIZATION POLICY

POLICY: Vecamyl™ (mecamylamine hydrochloride tablets – Vyera Pharmaceuticals)

DATE REVIEWED: 05/27/2020

OVERVIEW

Vecamyl is a nicotinic parasympathetic ganglionic blocker indicated for the management of moderately severe to severe essential hypertension and in uncomplicated cases of malignant hypertension.[1, 2] Vecamyl prevents stimulation of postsynaptic receptors by acetylcholine released from presynaptic nerve endings. The hypotensive effect of Vecamyl is attributed to reduction in sympathetic tone, vasodilation, and reduced cardiac output. Vecamyl is considered a nonselective antagonist that easily passes through the blood-brain barrier, and thus, having the potential to affect nicotinic acetylcholine receptors in the central nervous system.

Guidelines

The Clinical Practice Guidelines from the American College of Cardiology/American Heart Association Task Force (2017) state the prevalence of severe hypertension has been declining, but approximately 12.3% of US adults with hypertension have an average systolic blood pressure ≥ 160 mm Hg or average diastolic blood pressure ≥ 100 mm Hg.[3] Numerous classes of antihypertensive agents are available to treat high blood pressure. Vecamyl is not suggested as a primary or secondary agent in the treatment of hypertension. The Evidence-Based Guideline for the Management of High Blood Pressure in Adults from the panel members of the eighth joint national committee (2014 [JNC 8]) advise selection among four specific medication classes (thiazide-type diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers) as initial and secondary choices in treatment.[4]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Vecamyl. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vecamyl as well as the monitoring required for adverse events and long-term efficacy, approval requires Vecamyl to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vecamyl is recommended in those who meet the following criteria:

FDA-Approved Indications

268. Essential Hypertension, Moderately Severe to Severe. Approve for 1 year if the patient meets the following criteria (A):

A) The patient has tried four antihypertensive therapies each from different pharmacologic classes (e.g., diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers [as single-entity or as combination products]) and has had at least one of the following from each of these agents (i or ii)

i. The patient has had inadequate efficacy; OR

ii. The patient has experienced adverse event(s) severe enough to warrant discontinuation of this agent, according to the prescriber.

269. Uncomplicated Malignant Hypertension. Approve for 1 year if the patient meets the following criteria (A):

A) The patient has tried four antihypertensive therapies each from different pharmacologic classes (e.g., diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers [as single-entity or as combination products]) and has had at least one of the following from each of these agents (i or ii)

i. The patient has had inadequate efficacy; OR

ii. The patient has experienced adverse event(s) severe enough to warrant discontinuation of this agent, according to the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Vecamyl has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

23. Tourette Syndrome. Limited data are available to validate the use of mecamylamine in Tourette Syndrome. A clinical trial has shown mecamylamine to not be an effective treatment for tics or for the total spectrum of symptoms associated with Tourette Syndrome.[5]

24. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

833. Vecamyl™ oral tablets [prescribing information]. New York, NY: Vyera Pharmaceuticals; October 2018.

834. Nickell J, Grinevich V, Siripurapu K, et al. Potential therapeutic uses of mecamylamine and its stereoisomers. *Pharmacology Biochemistry and Behavior*. 2013; 108:28-43.

835. Whelton P, Carey R, Aronow W, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension.* 2018;71:e13-e115.

836. James P, Oparil S, Carter B, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report by the panel appointed to the Eighth Joint National Committee (JNC 8). *JAMA.* 2014;311:17:507-520.
837. Silver A, Shytle RD, Sheehan K, et al. Multicenter, double-blind, placebo-controlled study of mecamylamine monotherapy for Tourette's Disorder. *Journal of the American Academy of Child and Adolescent Psychiatry. 2001:40:9: 1103-1110.*

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	05/29/2019
Annual revision	**Essential Hypertension, Moderately Severe to Severe.** For the exception applying to patients that have experienced adverse event(s) severe enough to warrant discontinuation of this agent, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician). **Uncomplicated Malignant Hypertension.** For the exception applying to patients that have experienced adverse event(s) severe enough to warrant discontinuation of this agent, wording was updated to more generally allow this determination by the prescriber (criteria previously specified this was according to the prescribing physician).	05/27/2020

PRIOR AUTHORIZATION POLICY

POLICY: Veregen Prior Authorization Policy

- Veregen® (sinecatechins ointment – Fougera Pharmaceuticals)

REVIEW DATE: 01/13/2021

OVERVIEW

Veregen, a botanical drug product, is indicated for the topical treatment of **external genital and perianal warts** (*Condylomata acuminata*) in immunocompetent patients ≥ 18 years of age.[1]

Guidelines

The Centers for Disease Control and Prevention (CDC) Sexually Transmitted Diseases Treatment Guidelines (2015) detail the patient-applied and provider-applied treatment options for the management of genital warts.[2] The CDC guidelines note that treatment should be guided by wart size, number of lesions, location of the wart(s), the preference of the patient, cost of treatment, convenience, adverse effects, and the experience of the health care provider with the various provider-applied options. There is no definitive evidence available which has demonstrated the superiority of one product over others for all patients and all warts. Most patients will require a course of therapy vs. a single-treatment. Most warts will typically respond to therapy in 3 months, but if response does not occur, then treatment options should be reassessed and modified if needed. The CDC recommended patient-applied regimens include: imiquimod 3.75% cream (Zyclara, generics) or 5% cream (Aldara, generics), podofilox 0.5% solution or gel (Condylox, generics for solution available), or sinecatechins 15% ointment (Veregen). The CDC recommended provider-applied regimens include: cryotherapy with liquid nitrogen or cryoprobe, trichloroacetic acid or bichloroacetic acid 80-90%, or surgical removal by tangential scissor excision, tangential shave excision, curettage, or electrosurgery. Alternatives listed are podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Veregen. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Veregen is recommended in those who meet the following criteria:

FDA-Approved Indications

270. Genital or Perianal Warts, External. Approve for 4 months if the patient meets the following criteria (A, B, and C):

A) Patient is ≥ 18 years of age; AND

B) Patient is immunocompetent, according to the prescriber; AND

C) Patient has tried one other treatment for the management of external genital or perianal warts.
Note: Examples of treatment for the management of external genital or perianal warts include imiquimod cream, podofilox gel or solution, cryotherapy, trichloroacetic or bichloroacetic acid, surgical removal, podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Veregen is not recommended in the following situations:

272. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

421. Veregen® [prescribing information]. Melville, NY: Fougera Pharmaceuticals; February 2020.
422. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2015. *MMWR.* 2015;64(No. RR-3):1-140.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/15/2020
Annual Revision	No criteria changes.	01/13/2021

PRIOR AUTHORIZATION POLICY

POLICY: Vesicular Monoamine Transporter Type 2 Inhibitors – Austedo Prior Authorization Policy

- Austedo® (deutetrabenazine tablets – Teva)

REVIEW DATE: 06/10/2020; selected revision 01/20/2021

OVERVIEW

Austedo, a vesicular monoamine transporter type 2 (VMAT2) inhibitor, is indicated for the treatment of:[1]

- **Chorea associated with Huntington's disease** in adults.
- **Tardive dyskinesia** in adults.

Guidelines

According to the American Academy of Neurology (AAN) guidelines on the treatment of chorea of Huntington's disease (2012), if Huntington's disease chorea requires treatment, clinicians should prescribe

tetrabenazine (≤ 100 mg/day), amantadine (300 to 400 mg/day), or riluzole (200 mg/day) [Level B] for varying degrees of expected benefit.[2] Austedo is not addressed in the guidelines.

The AAN published an evidence-based guideline for the treatment of tardive syndromes (TDS) [2013].[3] The authors found that tetrabenazine possibly reduces TDS symptoms (based on two consistent Class III studies). Therefore, tetrabenazine may be considered in treating TDS (Level C). Austedo is not addressed in the guidelines.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Austedo. Because of the specialized skills required for evaluation and diagnosis of patients treated with Austedo as well as the monitoring required for adverse events and long-term efficacy, approval requires Austedo to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Documentation: Documentation is required for the use of Austedo as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Austedo is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Chorea Associated with Huntington's Disease.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has been diagnosed with chorea associated with Huntington's disease **[documentation required]**; AND
   - **C)** Diagnosis of Huntington's disease is confirmed by genetic testing (for example, an expanded HTT CAG repeat sequence of at least 36); AND
   - **D)** The medication is prescribed by or in consultation with a neurologist.

2. **Tardive dyskinesia.** Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** The medication is prescribed by or in consultation with a neurologist or psychiatrist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Austedo is not recommended in the following situations:

25. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

610. Austedo® tablets [prescribing information]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; July 2019.

611. Armstrong MJ, Miyasaki JM. Evidence-based guideline: pharmacologic treatment of chorea in Huntington disease: report of the guideline development subcommittee of the American Academy of Neurology. *Neurology.* 2012;79:597-603.
612. Bhidayasiri R, Fahn S, Weiner WJ, et al. Evidence-based guideline: treatment of tardive syndromes: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* 2013;81(5):463-469.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	No change to criteria.	04/25/2018
Annual revision	No change to criteria.	05/22/2019
Annual revision	No change to criteria.	06/10/2020
Selected Revision	**Chorea Associated with Huntington's Disease:** Added criteria for age ≥ 18 years and diagnosis of Huntington's disease confirmed by genetic testing (for example, an expanded HTT CAG repeat sequence of at least 36). **Tardive dyskinesia:** Added criteria for age ≥ 18 years.	01/20/2021

PRIOR AUTHORIZATION POLICY

POLICY: Vesicular Monoamine Transporter Type 2 Inhibitors – Ingrezza Prior Authorization Policy
- Ingrezza® (valbenazine capsules – Neurocrine Biosciences)

REVIEW DATE: 06/10/2020; selected revision 01/20/2021

OVERVIEW
Ingrezza, a vesicular monoamine transporter type 2 (VMAT2) inhibitor, is indicated for the treatment of **tardive dyskinesia** in adults.[1]

POLICY STATEMENT
Prior Authorization is recommended for prescription benefit coverage of Ingrezza. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ingrezza as well as the monitoring required for adverse events and long-term efficacy, approval requires Ingrezza to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Ingrezza is recommended in those who meet the following criteria:

FDA-Approved Indications

3. Tardive Dyskinesia. Approve for 1 year if the patient meets the following criteria (A and B):
- **2.** Patient is ≥ 18 years of age; AND
- **3.** The medication is prescribed by or in consultation with a neurologist or psychiatrist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Ingrezza is not recommended in the following situations:

26. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

613. Ingrezza® capsules [prescribing information]. San Diego, CA: Neurocrine Biosciences, Inc.; April 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No change to criteria.	04/25/2018
Annual Revision	No change to criteria.	05/22/2019
Annual Revision	No change to criteria.	06/10/2020
Selected Revision	**Tardive dyskinesia:** Added criteria for age ≥ 18 years.	01/20/2021

PRIOR AUTHORIZATION POLICY

POLICY: Vesicular Monoamine Transporter Type 2 Inhibitors – Tetrabenazine Prior Authorization Policy

- Xenazine® (tetrabenazine tablets – Lundbeck, generics)

REVIEW DATE: 06/10/2020; selected revision 01/20/2021

OVERVIEW

Tetrabenazine, a vesicular monoamine transporter type 2 (VMAT2) inhibitor, is indicated for the treatment of **chorea associated with Huntington's disease** in adults.[1]

Beginning in September 2015, tetrabenazine has been available as an AB-rated generic to brand Xenazine. Generic tetrabenazine is FDA-approved and is available in the same tablet dosage form and the same 12.5 mg and 25 mg strengths as brand Xenazine.

Clinical Efficacy

There are multiple controlled and uncontrolled trials conducted with tetrabenazine that included patients with dystonias.[6-10,12,13,16,19,21,22] In retrospective trials, an overall moderate clinical improvement or better was seen in 161 out of 163 patients with dystonia treated with tetrabenazine.[21] A treatment algorithm for secondary dystonias was developed that notes tetrabenazine can be tried following a trial of an anticholinergic in children with severe secondary dystonias.[22] In adults, tetrabenazine can be tried (alone or as combination therapy) following a low-dose trial of anticholinergic.

Tetrabenazine has been studied for the treatment of tardive dyskinesia, either as initial therapy or in patients who have responded poorly to other agents (e.g., reserpine, bromocriptine, clozapine).[5-15]

While most of the data for treatment of Tourette syndrome indicate that antipsychotic medications, both typical and atypical, are most effective, other medications (including tetrabenazine) may be used first to avoid the potential side effects of dopamine blockade.[18]

Guidelines

The American Academy of Neurology (AAN) evidence-based guidelines on pharmacologic treatment of chorea in Huntington's disease (2012) states that if chorea in Huntington's disease requires treatment, clinicians should prescribe tetrabenazine, amantadine, or Rilutek® (riluzole tablets) [Level B].[2]

The AAN published an evidence-based guideline for the treatment of tardive syndromes (TDS) [2013].[3] The authors found that tetrabenazine possibly reduces TDS symptoms (based on two consistent Class III studies). Therefore, tetrabenazine may be considered in treating TDS (Level C).

The AAN published practice guideline recommendations for the treatment of tics in people with Tourette syndrome and chronic tic disorders (2019).[4] The guidelines state that the dopamine depleters, tetrabenazine, deutetrabenazine, and valbenazine, are lacking published, randomized, controlled trials in the treatment of tics but note that these drugs are increasingly used off-label. When appropriately dosed, these drugs are generally well-tolerated but may be associated with drowsiness, depression, and parkinsonism.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of tetrabenazine. Because of the specialized skills required for evaluation and diagnosis of patients treated with tetrabenazine as well as the monitoring required for adverse events and long-term efficacy, approval requires tetrabenazine to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of tetrabenazine is recommended in those who meet the following criteria:

FDA-Approved Indications

4. **Chorea Associated with Huntington's Disease.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **C)** Patient is ≥ 18 years of age; AND
   - **61.** Diagnosis of Huntington's disease is confirmed by genetic testing (for example, an expanded HTT CAG repeat sequence of at least 36); AND
   - **62.** The medication is prescribed by or in consultation with a neurologist.

Other Uses with Supportive Evidence

5. **Hyperkinetic Dystonia.** Approve for 1 year if the patient meets the following criteria (A and B):
   - **4.** Patient is ≥ 18 years of age; AND
   - **5.** The medication is prescribed by or in consultation with a neurologist.

6. **Tardive Dyskinesia.** Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** The medication is prescribed by or in consultation with a neurologist or psychiatrist.

7. **Tourette Syndrome and Related Tic Disorders.** Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** The medication is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of tetrabenazine is not recommended in the following situations:

27. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

614. Xenazine® tablets [prescribing information]. Deerfield, IL: Lundbeck; September 2017.
615. Armstrong MJ, Miyasaki JM. Evidence-based guideline: pharmacologic treatment of chorea in Huntington disease: report of the guideline development subcommittee of the American Academy of Neurology. *Neurology.* 2012;79:597-603.
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617. Pringsheim T, Okun MS, Müller-Vahl K, et al. Practice guideline recommendations summary: treatment of tics in people with Tourette syndrome and chronic tic disorders. *Neurology*. 2019;92:896-906.
618. Kenney C, Jankovic J. Tetrabenazine in the treatment of hyperkinetic movement disorders. *Expert Rev Neurotherapeutics.* 2006;6:7-17.
619. IBM Micromedex®. IBM Corporation. Available at: www.micromedexsolutions.com. Accessed on June 7, 2020. Search terms: tetrabenazine.
620. Jankovic J, Orman J. Tetrabenazine therapy of dystonia, chorea, tics, and other dyskinesias. *Neurology.* 1988;38:391-394.
621. Kenney C, Hunter C, Jankovic J. Long-term tolerability of tetrabenazine in the treatment of hyperkinetic movement disorders. *Mov Disord.* 2007;22:193-197.
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624. Ondo WG, Hanna PA, Jankovic J. Tetrabenazine treatment for tardive dyskinesia: assessment by randomized videotape protocol. *Am J Psychiatry*. 1999;156:1279-1281.
625. Jankovic J. Treatment of hyperkinetic movement disorders with tetrabenazine: a double-blind crossover study. *Ann Neurol*. 1982;11(1):41-47.
626. Asher SW, Aminoff MJ. Tetrabenazine and movement disorders. *Neurology*. 1981;31(8):1051-1053.
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628. Kazamatsuri H, Chien C, Cole JO. Treatment of tardive dyskinesia: clinical efficacy of a dopamine-depleting agent, tetrabenazine. *Arch Gen Psychiat*. 1972;27:95-99.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No changes to criteria.	04/25/2018
Selected Revision	Removal of the requirement for a previous trial of generic tetrabenazine if brand Xenazine is requested. This is due to a new VMAT2 Inhibitor Preferred Specialty Management policy.	08/29/2018
Annual Revision	No change to criteria.	05/22/2019
Annual Revision	No change to criteria.	06/10/2020
Selected Revision	**Chorea Associated with Huntington's Disease:** Added criteria for age ≥ 18 years and diagnosis of Huntington's disease confirmed by genetic testing (for example, an expanded HTT CAG repeat sequence of at least 36). **Hyperkinetic Dystonia:** Added criteria for age ≥ 18 years. **Tardive dyskinesia:** Added criteria for age ≥ 18 years.	01/20/2021

	Tourette Syndrome and Related Tic Disorders: Added criteria for age ≥ 18 years.	

PRIOR AUTHORIZATION POLICY

POLICY: Wakefulness-Promoting Agents – Armodafinil, Modafinil Prior Authorization Policy
- Nuvigil® (armodafinil tablets – Cephalon, generics)
- Provigil® (modafinil tablets – Cephalon, generics)

REVIEW DATE: 09/09/2020

OVERVIEW

Armodafinil and modafinil, agents with wake-promoting actions that are similar to sympathomimetic agents (e.g., amphetamine and methylphenidate), are indicated **to improve wakefulness in adults with** the following conditions:[1,2]

- **Excessive sleepiness associated with narcolepsy**.
- **Obstructive sleep apnea/hypoapnea syndrome** (approved as adjunctive therapy).
- **Shift work sleep disorder**.

Armodafinil and modafinil are Schedule IV controlled substances.[1,2] Review of the medical literature notes many other uses of modafinil that are considered off-label or investigational. While armodafinil has not been studied off-label to the same extent as modafinil, it is expected that armodafinil will have similar clinical efficacy for these uses.

Two specialized tests, which can be performed in a sleep disorders clinic, are required to establish a diagnosis of narcolepsy.[46] Polysomnography is an overnight recording of brain and muscle activity, breathing, and eye movements. The multiple sleep latency test (MSLT) assesses daytime sleepiness by measuring how quickly a person falls asleep and whether they enter rapid eye movement (REM) sleep. Polysomnography is routinely indicated for the diagnosis of sleep-related breathing disorders; for continuous positive airway pressure titration in patients with sleep-related breathing disorders; with a MSLT in the evaluation of suspected narcolepsy; and in certain atypical or unusual parasomnias.[47] The MSLT is indicated as part of the evaluation of patients with suspected narcolepsy to confirm the diagnosis. Most patients with narcolepsy have objective evidence of hypersomnia as determined by a mean sleep latency < 5 minutes. In studies, the presence of two or more sleep-onset REM episodes (SOREMPs) was associated with a sensitivity of 0.78 and a specificity of 0.93 for the diagnosis of narcolepsy. SOREMPs do not occur exclusively in patients with narcolepsy, and thus it is important to rule out or treat other sleep disorders before evaluating SOREMPs in the diagnosis of narcolepsy. For this reason, polysomnography and a MSLT performed on the day after the polysomnographic evaluation are routinely indicated in the evaluation of suspected narcolepsy.

Guidelines

According to the American Academy of Sleep Medicine (AASM), continuous positive airway pressure (CPAP) is the most uniformly effective therapy, and, to date, this is the only intervention for obstructive sleep apnea (OSA) shown to have favorable impacts on both cardiovascular and neurobehavioral morbidities.[3] Modafinil, in patients compliant with nasal CPAP, consistently improved subjective and objective sleepiness, quality of life, and vigilance compared with placebo.

According to the American Psychiatric Association (APA) practice guideline for the treatment of patients with major depressive disorder (MDD), modafinil (or methylphenidate) are potential treatments for sedation associated with antidepressant medications.[4] The APA guidelines state that modafinil has shown benefit

when combined with a selective serotonin reuptake inhibitor (SSRI), related to specific effects on residual symptoms such as fatigue and hypersomnolence. The guidelines go on to note that there is no clear guidance regarding the length of time modafinil should be coadministered. Limited data have investigated modafinil as monotherapy for depression.[5] While armodafinil has not been studied for this use, expert opinion considers it to be interchangeable with modafinil for this condition.

Practice parameters from the AASM, last updated in 2007, state that modafinil may be effective for the treatment of daytime sleepiness due to myotonic dystrophy.[12] Results from clinical trials evaluating the effectiveness of modafinil in treating excessive daytime sleepiness associated with myotonic dystrophy are heterogeneous.[7-11] While armodafinil has not been studied for this use, expert opinion considers it to be interchangeable with modafinil for this condition.

Practice parameters from the AASM (2007) state that modafinil may be effective for the treatment of daytime sleepiness due to Parkinson's disease.[12] A practice parameter on the treatment of nonmotor symptoms of Parkinson's disease, published by the American Academy of Neurology (AAN) in 2011, states that for patients with Parkinson's disease and excessive daytime sleepiness, modafinil is effective in improving patients' perception of wakefulness, but is ineffective in objectively improving excessive daytime sleepiness as measured by objective tests.[15] The practice parameter recommendations indicate modafinil should be considered for patients to improve their subjective perception of excessive daytime sleepiness; however, it should be noted that patients may experience an improvement in sleep perception without an actual improvement in objective sleep measurements. Reviews addressing excessive daytime sleepiness and Parkinson's disease recommended modafinil along with other agents such as bupropion and dextroamphetamine, although published data with the latter are limited.[13,14] While armodafinil has not been studied for this use, expert opinion considers it to be interchangeable with modafinil for this condition.

Practice parameters from the AASM (2007) state that modafinil may be effective for the treatment of fatigue due to multiple sclerosis.[12] Although the results with modafinil in clinical trials are heterogeneous, expert opinion considers it to be a first-line anti-fatigue drug for multiple sclerosis patients. While armodafinil has not been studied for this use, expert opinion considers it to be interchangeable with modafinil for this condition.

Idiopathic hypersomnia, a condition similar to narcolepsy, is characterized by constant or recurrent daytime sleepiness with no other cause of sleepiness, prolonged nocturnal sleep, difficulty awakening with sleep drunkenness, and long unrefreshing naps with no history of cataplexy.[17-19] Practice parameters from the AASM (2007) state that modafinil may be effective for the treatment of daytime sleepiness due to idiopathic hypersomnia.[12] As there may be underlying causes/behaviors associated with excessive daytime sleepiness, a sleep specialist physician has the training to correctly recognize and diagnose this condition. While armodafinil has not been studied for this use, expert opinion considers it to be interchangeable with modafinil for this condition.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Nuvigil (brand and generic) and Provigil (brand and generic). All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of modafinil (brand and generic) and armodafinil (brand and generic) is recommended in those who meet the following criteria:

FDA-Approved Indications

27. Excessive Daytime Sleepiness Associated with Obstructive Sleep Apnea/Hypoapnea Syndrome. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets one of the following criteria (i or ii):
  - **i.** Armodafinil/modafinil will be used in conjunction with continuous positive airway pressure; OR
  - **ii.** Patient is unable to initiate or tolerate continuous positive airway pressure therapy; AND
- **C)** If brand Provigil or Nuvigil is being requested, the patient meets both of the following criteria (i and ii):
  - **i.** Patient has tried generic modafinil or generic armodafinil; AND
  - **ii.** Brand product (Nuvigil or Provigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

28. Excessive Sleepiness Associated with Shift Work Sleep Disorder. Approve for 1 year if the patient meets the following criteria (A, B and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient works at least five overnight shifts per month; AND
- **C)** If brand Provigil or Nuvigil is being requested, the patient meets both of the following criteria (i and ii):
  - **i.** Patient has tried generic modafinil or generic armodafinil; AND
  - **ii.** Brand product (Nuvigil or Provigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

29. Excessive Daytime Sleepiness Associated with Narcolepsy. Approve for 1 year if the patient meets both of the following criteria (A, B, C and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has been evaluated using polysomnography and a multiple sleep latency test (MSLT); AND
- **C)** Diagnosis of narcolepsy has been confirmed, according to the prescriber; AND
- **D)** If brand Provigil or Nuvigil is being requested, the patient meets both of the following criteria (i and ii):
  - **i.** Patient has tried generic modafinil or generic armodafinil; AND
  - **ii.** Brand product (Nuvigil or Provigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

Other Uses with Supportive Evidence

~~30.~~ Adjunctive/Augmentation Treatment for Depression in Adults. Approve for 1 year if the patient meets the following criteria (A, B and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient is concurrently receiving other medication therapy for depression; AND

Note: Examples of other medications for the treatment of depression include selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs).

C) If brand Provigil or Nuvigil is being requested, the patient meets both of the following criteria (i and ii):

i. Patient has tried generic modafinil or generic armodafinil; AND

ii. Brand product (Nuvigil or Provigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

~~31.~~ **Excessive Daytime Sleepiness Associated with Myotonic Dystrophy.** Approve for 1 year if the patient meets both of the following criteria (A and B):

A) Patient is ≥ 18 years of age; AND

B) If brand Provigil or Nuvigil is being requested, the patient meets both of the following criteria (i and ii):

i. Patient has tried generic modafinil or generic armodafinil; AND

ii. Brand product (Nuvigil or Provigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

~~32.~~ **Excessive Daytime Sleepiness Associated with Parkinson's Disease.** Approve for 1 year if the patient meets both of the following criteria (A and B):

A) Patient is ≥ 18 years of age; AND

B) If brand Provigil or Nuvigil is being requested, the patient meets both of the following criteria (i and ii):

i. Patient has tried generic modafinil or generic armodafinil; AND

ii. Brand product (Nuvigil or Provigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

~~33.~~ **Fatigue Associated with Multiple Sclerosis.** Approve for 1 year if the patient meets both of the following criteria (A and B):

A) Patient is ≥ 18 years of age; AND

B) If brand Provigil or Nuvigil is being requested, the patient meets both of the following criteria (i and ii):

i. Patient has tried generic modafinil or generic armodafinil; AND

ii. Brand product (Nuvigil or Provigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

~~34.~~ **Idiopathic Hypersomnia.** Approve for 1 year if the patient meets both of the following (A, B and C):

~~a)~~ Patient is ≥ 18 years of age; AND

~~b)~~ The diagnosis is confirmed by a sleep specialist physician or at an institution that specializes in sleep disorders (i.e., sleep center); AND

~~c)~~ If brand Provigil or Nuvigil is being requested, the patient meets both of the following criteria (i and ii):

i. Patient has tried generic modafinil or generic armodafinil; AND
ii. Brand product (Nuvigil or Provigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of modafinil (brand and generic) and armodafinil (brand and generic) is not recommended in the following situations:

14. **Attention Deficit Hyperactivity Disorder (ADHD).** The American Academy of Pediatrics (AAP) clinical practice guidelines for the treatment of ADHD in children and adolescents (2011 and 2019) do not address the use of modafinil/armodafinil.[20,21] These guidelines note that with the greater availability of approved medications for children/adolescents with ADHD, it has become increasingly unlikely that clinicians need to consider the off-label use of other medications. Two published studies, both of which involved approximately 20 adults with ADHD, preliminarily suggested that modafinil may be useful for this condition.[22,23] However, a 9-week, randomized, double-blind, placebo-controlled, parallel-group, dose-finding study in adults with ADHD (n = 338) evaluated modafinil doses of 255 mg to 510 mg and did not find significant benefit in reducing ADHD symptoms, as measured by the change from baseline at final visit in the Adult ADHD Investigator Symptom Rating Scale (AISRS) total score.[24] Many options exist for the treatment of ADHD in adults (e.g., methylphenidate, dextroamphetamine) and further large scale trials that demonstrate benefit for modafinil in adults with ADHD are needed.

15. **Bipolar Disorder, including Bipolar Depression.** Limited data (one small study [n = 85] and case reports [n = 2]) are available that describe the use of modafinil for bipolar disorder and bipolar depression.[25-27] In one study (n = 257) armodafinil was not more effective than placebo in treating bipolar depression.[28] Only limited data supports modafinil for this condition and more data are needed.

16. **Cancer-Related Fatigue.** The National Comprehensive Cancer Network (NCCN) guidelines on cancer-related fatigue (version 2.2020 – May 4, 2020) no longer consider modafinil to be effective for the treatment of cancer-related fatigue and recommend against its use.[16] A randomized, double-blind, placebo-controlled trial involving 631 patients with cancer receiving chemotherapy found modafinil useful in the control of severe cancer-related fatigue only.[6] Other studies do not support the use of modafinil or armodafinil for cancer-related fatigue.[42-44]

17. **Chronic Fatigue Syndrome.** Limited data characterize modafinil therapy in those with chronic fatigue syndrome.[29] In a randomized, double-blind, crossover study in 14 patients with chronic fatigue syndrome, use of modafinil for 20 days had minimal effects on cognitive function and no significant effects on fatigue, health-related quality of life, or mood.[30] More data are required to assess efficacy in this patient population.

18. **Excessive Daytime Sleepiness Associated with Primary Insomnia.** One randomized, placebo-controlled study found that neither combination therapy with modafinil and cognitive behavioral therapy nor modafinil as monotherapy significantly decreased daytime sleepiness associated with primary insomnia.[31]
19. **Enhancement of Performance in Situations of Induced Sleep Deprivation.** Studies are needed to define the role/appropriateness of modafinil in these situations for the general population (as opposed to military personnel, etc.). Studies have shown that modafinil may enhance performance and sustain alertness in individuals subjected to situations that deprive sleep (e.g., military aviation, emergency

physicians).[32-35] Further studies are needed before its use in the general population in these types of situations can be promoted.

20. **Fatigue and Excessive Daytime Sleepiness in Chronic Traumatic Brain Injury.** A single-center, double-blind, placebo- controlled, crossover trial involving 53 patients suggests that overall, modafinil was not beneficial in relieving fatigue and excessive daytime sleepiness in such patients.[36] In a small (n = 20) randomized, placebo-controlled trial, modafinil improved excessive daytime sleepiness vs. placebo in patients with traumatic brain injury; however, modafinil did not improve fatigue compared with placebo.[37] Additional data are needed to determine effectiveness in this setting.

21. **Fibromyalgia.** Limited data are available regarding the use of modafinil in fibromyalgia with most of the data being observational.[38-40] Larger-sized, randomized, placebo-controlled trials are required to better assess and validate the efficacy of modafinil in patients with fibromyalgia before it can be recommended as a therapeutic modality.

22. **Hypersomnia, Fatigue or Sleepiness Due to Other Conditions (<u>not</u> Idiopathic Hypersomnia, see Other Uses with Supportive Evidence).** More data are needed in specific conditions to define the role of modafinil and armodafinil.

23. **Post-Stroke Sleep-Wake Disorders or Sleep Disorders.** Sleep-wake disorders occur in approximately 20% to 40% of patients that have experienced a stroke, which includes hypersomnia and excessive daytime sleepiness. Very limited data (i.e., case reports and one small study) have explored the use of modafinil in these patients to improve alertness.[41,45] More data are needed to determine effectiveness in this condition.

24. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Update	08/02/2019: Change in the policy name to add the descriptor "Wakefulness-Promoting Agents".	--
Annual Revision	Addition to all approval conditions that requires the patient to have tried generic modafinil or armodafinil if brand Nuvigil or Provigil is being requested AND that the brand product (Provigil or Nuvigil) is being requested due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the Brand and the corresponding generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction. The policy name was changed from Wakefulness-Promoting Agents – Nuvigil, Provigil to Wakefulness-Promoting Agents – Armodafinil, Modafinil. Removal of automation using ICD-9/ICD-10 codes for narcolepsy without cataplexy and narcolepsy in conditions classified elsewhere without cataplexy to allow approval of the requested medication.	08/21/2019
Selected Revision	Criteria stating that "the patient is ≥ 18 years of age" was added to each of the approval conditions. Patient < 17 years of age was removed from the Conditions Not Recommended for Approval. Added "Excessive Daytime Sleepiness Associated with" to the approval criteria for **Narcolepsy** and also added a requirement that narcolepsy has been confirmed with polysomnography and a multiple sleep latency test (MSLT). Inserted "Daytime" in Excessive Sleepiness and changed "Due to" to "Associated with" for the approval conditions of **Obstructive Sleep Apnea/Hypoapnea Syndrome**, **Shift Work Sleep Disorder**, **Myotonic Dystrophy**, and **Parkinson's Disease**.	03/25/2020
Selected Revision	Removal of the approval condition of **Fatigue or sleepiness associated with chronic use of narcotic analgesics in patients with cancer**. For approval condition of **Excessive Daytime Sleepiness Associated with Shift Work Sleep Disorder**, the word Daytime was removed since these people may use the medication to stay awake during their shift work at night. Under Conditions Not Recommended for Approval, "**Adjunctive therapy in the treatment of schizophrenia**" and "**Spasticity due to cerebral palsy**" were removed.	05/20/2020
Annual Revision	For the approval condition of **Excessive Daytime Sleepiness Associated with Narcolepsy**, the criterion of "Narcolepsy has been confirmed with polysomnography and a multiple sleep latency test (MSLT)" was split into two criteria: "Patient has been evaluated using polysomnography and a multiple sleep latency test (MSLT)" and "Diagnosis of narcolepsy has been confirmed, according to the prescriber". For the approval condition of **Adjunctive/Augmentation Treatment for Depression in Adults**, examples of antidepressant medications were moved to a note.	09/09/2020

PRIOR AUTHORIZATION POLICY WITH STEP THERAPY

POLICY: Wakefulness-Promoting Agents – Sunosi Prior Authorization Policy with Step Therapy

- Sunosi™ (solriamfetol tablets – Jazz Pharmaceuticals)

REVIEW DATE: 07/29/2020

OVERVIEW

Sunosi, a dopamine and norepinephrine reuptake inhibitor (DNRI), is indicated to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (OSA).[1] Limitations of Use: Sunosi is not indicated to treat the underlying airway obstruction in OSA. The underlying airway obstruction should be treated (e.g., with continuous positive airway pressure [CPAP]) for at least 1 month prior to initiating Sunosi for excessive daytime sleepiness. Modalities to treat the underlying airway obstruction should be continued during treatment with Sunosi. Sunosi is not a substitute for these modalities. The mechanism of action of Sunosi to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy or OSA is unclear. Its efficacy is thought to be mediated through its activity as an inhibitor of dopamine and norepinephrine reuptake. Sunosi is a schedule IV controlled substance.

Armodafinil and modafinil are wakefulness-promoting agents with actions similar to sympathomimetic agents (e.g., amphetamine and methylphenidate). They are indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, OSA, or shift work disorder (SWD).[2,3] Armodafinil and modafinil are Schedule IV controlled substances. For narcolepsy and OSA, they are dosed QD in the morning. For SWD, they are dosed QD as a single dose approximately 1 hour prior to the start of their work shift. Stimulant medications (e.g., amphetamine, methamphetamine, dextroamphetamine, and methylphenidate) are used off-label for the treatment of daytime sleepiness due to narcolepsy and OSA and are mentioned in guidelines.[4-7]

Disease Overview

Narcolepsy is a rare, chronic neurologic disorder that affects the brain's ability to control sleep-wake cycles.[8] There are two types of narcolepsy: Type 1 narcolepsy (previously termed narcolepsy with cataplexy) and Type 2 narcolepsy (previously termed narcolepsy without cataplexy). People with narcolepsy usually feel rested after waking, but then feel very sleepy throughout much of the day. Sleepiness in narcolepsy is described as a "sleep attack", where an overwhelming sense of sleepiness comes on quickly. People may unwillingly fall asleep even if they are in the middle of an activity like driving, eating, or talking. Symptoms can partially improve over time, but they will never disappear completely. If left undiagnosed or untreated, narcolepsy can interfere with psychological, social, and cognitive function and development and can inhibit academic, work, and social activities.

Two specialized tests, which can be performed in a sleep disorders clinic, are required to establish a diagnosis of narcolepsy.[8] Polysomnogram (PSG) is an overnight recording of brain and muscle activity, breathing, and eye movements. The multiple sleep latency test (MSLT) assesses daytime sleepiness by measuring how quickly a person falls asleep and whether they enter rapid eye movement (REM) sleep. On the day after PSG, the patient is asked to take five short naps separated by two hours over the course of a day. If an individual falls asleep in < 8 minutes on average over the five naps, this indicates excessive daytime sleepiness. However, patients with narcolepsy also have an abnormally quick start to REM sleep. If REM sleep happens within 15 minutes at least two times out of the five naps and the sleep study the night before, this is likely an abnormality caused by narcolepsy.

OSA is a potentially serious sleep disorder, causing breathing to repeatedly stop and start during sleep.[9] Several types of sleep apnea occur, but the most common is OSA. OSA occurs when the muscles in the back of the throat relax too much, inhibiting normal breathing. When the muscles relax, the airway narrows or closes. Breathing may be inadequate for 10 to 20 seconds, lowering the level of oxygen in the blood and causing a buildup of carbon dioxide. The brain senses this impaired breathing and briefly rouses the patient from sleep so that the airway can be reopened. This pattern can repeat itself five to 30 times or more each hour, throughout the night. The disruptions impair the ability to reach the desired deep, restful phases of sleep, resulting in a sleepy feeling during the waking hours. OSA can cause severe daytime drowsiness, fatigue, and irritability; hypertension, which can increase the risk of coronary artery disease, heart attack, heart failure and stroke; and arrhythmias.

CPAP is the most uniformly effective therapy, and to date this is the only intervention for OSA shown to have a favorable impact on both cardiovascular and neurobehavioral morbidities.[6] Oral appliances and surgical procedures to improve upper airway patency are successful in certain subsets of patients, but many do not receive adequate clinical benefit from these approaches. In addition, individuals treated with CPAP therapy may experience residual sleepiness, despite marked improvements in the apnea-hypopnea index. Therefore, medical therapies may be considered for the subsets of patients who will not or cannot use CPAP and for patients with residual sleepiness despite alleviation of upper airway obstruction during sleep by CPAP, oral appliances, or upper airway surgery.

Guidelines

The American Academy of Sleep Medicine (AASM) practice parameters for the treatment of narcolepsy and other hypersomnias of central origin (2007) list modafinil as an effective for treatment of daytime sleepiness due to narcolepsy (Standard) and Xyrem as effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy (Standard).[4,5] At the time this practice parameter was written, published studies involving armodafinil were limited.

The AASM has published recommendations for the medical therapy of OSA (2006).[6,7] CPAP is the most uniformly effective therapy and is the only intervention for OSA shown to have favorable impacts on both cardiovascular and neurobehavioral morbidities. When the recommendation was published, there were no widely effective pharmacotherapies for individuals with sleep apnea, with the important exceptions of individuals with hypothyroidism or with acromegaly. Treating the underlying medical condition can have pronounced effects on the apnea/hypopnea index. Stimulant therapy leads to a small but statistically significant improvement in objective sleepiness.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Sunosi. This PA Policy also contains a Step Therapy component. When clinically appropriate, patients are directed to try one Step 1 agent (modafinil or armodafinil) prior to Sunosi (Step 2). All approvals are provided for the duration cited.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Sunosi is recommended in those who meet the following criteria:
FDA-Approved Indications

35. Excessive Daytime Sleepiness Associated with Obstructive Sleep Apnea. Approve for 1 year if the patient meets one of the following criteria (A, B and C):
- **D)** Patient is ≥ 18 years of age; AND
- **E)** Patient meets one of the following criteria (i or ii):
  - **i.** Sunosi will be used in conjunction with continuous positive airway pressure (CPAP); OR
  - **ii.** Patient is unable to initiate or tolerate CPAP therapy; AND
- **F)** Patient has tried generic modafinil or generic armodafinil.
  Note: An exception to this requirement is allowed if the patient has previously tried brand Provigil or Nuvigil.

271. Excessive Daytime Sleepiness Associated with Narcolepsy. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Narcolepsy has been confirmed with polysomnography and a multiple sleep latency test (MSLT); AND
- **C)** Patient has tried generic modafinil or generic armodafinil.
  Note: An exception to this requirement is allowed if the patient has previously tried brand Provigil or Nuvigil.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Sunosi is not recommended in the following situations:

273. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/10/2019
Selected revision	For both of the approval conditions (Excessive Sleepiness Due to Obstructive Sleep Apnea and Narcolepsy), addition of requirement to have tried generic modafinil or generic armodafinil. An exception to this requirement is allowed if the patient has previously tried brand Provigil or Nuvigil.	08/21/2019
Selected revision	Criteria stating that "the patient is ≥ 18 years of age" was added to each of the approval conditions. Added "Excessive Daytime Sleepiness Associated with" to the approval criteria for narcolepsy and also added a requirement that narcolepsy has been confirmed with polysomnography and a multiple sleep latency test (MSLT). Inserted "Daytime" in Excessive Sleepiness and changed "Due to" to "Associated with" for the approval condition of Obstructive Sleep Apnea.	03/25/2020
Annual revision	No change to criteria.	07/29/2020

PRIOR AUTHORIZATION POLICY WITH STEP THERAPY

POLICY: Wakefulness-Promoting Agents – Wakix Prior Authorization Policy with Step Therapy

- Wakix® (pitolisant tablets – Harmony)

REVIEW DATE: 09/09/2020; selected revision 10/28/2020

OVERVIEW

Wakix is indicated for the treatment of:[1]

- **Excessive daytime sleepiness in adults with narcolepsy**.
- **Cataplexy in adults with narcolepsy**.

Wakix is an antagonist/inverse agonist of the histamine-3 (H_3) receptor.[1] Wakix should be titrated up to the recommended dosage range of 17.8 mg to 35.6 mg once daily (QD) in the morning upon wakening. The dose may be adjusted based on patient tolerability. For some patients, it may take up to 8 weeks to achieve a clinical response. Wakix is the only wakefulness-promoting agent that is not a controlled substance.

Armodafinil and modafinil are wakefulness-promoting agents with actions similar to sympathomimetic agents (e.g., amphetamine and methylphenidate). They are indicated to improve wakefulness in adults with excessive sleepiness associated with narcolepsy, obstructive sleep apnea (OSA), or shift work disorder (SWD).[2,3] For narcolepsy and OSA, they are dosed QD in the morning. For SWD, they are dosed QD as a single dose approximately 1 hour prior to the start of their work shift. Sunosi™ (solriamfetol tablets), a dopamine and norepinephrine reuptake inhibitor (DNRI), is indicated to improve wakefulness in adults with excessive daytime sleepiness associated with narcolepsy or OSA.[4] Sunosi whould be titrated to the recommended dose range of 37.5 mg to 150 mg QD, taken upon awakening with or without food. Sunosi should be avoided within 9 hours of planned bedtime because of the potential to interfere with sleep if taken too late in the day. Armodafinil, modafinil, and Sunosi are Schedule IV controlled substances.[2-4] Armodafinil, modafinil, and Sunosi are not indicated for the treatment of cataplexy.

Two specialized tests, which can be performed in a sleep disorders clinic, are required to establish a diagnosis of narcolepsy.[7] Polysomnography is an overnight recording of brain and muscle activity, breathing, and eye movements. The multiple sleep latency test (MSLT) assesses daytime sleepiness by measuring how quickly a person falls asleep and whether they enter rapid eye movement (REM) sleep. Polysomnography is routinely indicated for the diagnosis of sleep-related breathing disorders; for continuous positive airway pressure titration in patients with sleep-related breathing disorders; with a MSLT in the evaluation of suspected narcolepsy; and in certain atypical or unusual parasomnias.[8] The MSLT is indicated as part of the evaluation of patients with suspected narcolepsy to confirm the diagnosis. Most patients with narcolepsy have objective evidence of hypersomnia as determined by a mean sleep latency < 5 minutes. In studies, the presence of two or more sleep-onset REM episodes (SOREMPs) was associated with a sensitivity of 0.78 and a specificity of 0.93 for the diagnosis of narcolepsy. SOREMPs do not occur exclusively in patients with narcolepsy, and thus it is important to rule out or treat other sleep disorders before evaluating

SOREMPs in the diagnosis of narcolepsy. For this reason, polysomnography and a MSLT performed on the day after the polysomnographic evaluation are routinely indicated in the evaluation of suspected narcolepsy.

Guidelines

The American Academy of Sleep Medicine (AASM) published practice parameters in 2007 for the treatment of narcolepsy with and without cataplexy and other hypersomnias of central origin.[5,6] It should be noted that the guidelines are dated and do not include more recently-approved medications. Modafinil is listed as an effective for treatment of daytime sleepiness due to narcolepsy and Xyrem as effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy. Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are considered effective for the treatment of daytime sleepiness due to narcolepsy. Tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and venlafaxine may be effective for the treatment of cataplexy. Selegiline may be an effective treatment for cataplexy and daytime sleepiness.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Wakix. This Prior Authorization Policy also contains a Step Therapy component. When clinically appropriate, patients are directed to try one Step 1 agent (modafinil or armodafinil for excessive daytime sleepiness in narcolepsy; a tricyclic antidepressant, an SSRI, or venlafaxine for cataplexy in narcolepsy) prior to Wakix (Step 2). All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Wakix is recommended in those who meet the following criteria:

FDA-Approved Indications

36. Excessive Daytime Sleepiness Associated with Narcolepsy. Approve for 1 year if the patient meets one of the following criterion (A, B, C, and D):
- **a)** Patient is ≥ 18 years of age; AND
- **b)** Patient has been evaluated using polysomnography and a multiple sleep latency test (MSLT); AND
- **c)** Diagnosis of narcolepsy has been confirmed, according to the prescriber; AND
- **d)** Patient meets one of the following criteria (i or ii):
  - **i.** Patient has tried generic modafinil or generic armodafinil; OR
    Note: An exception to this requirement is allowed if the patient has previously tried brand Provigil or Nuvigil.
  - **ii.** Patient has a history of misuse or abuse of controlled substances and a wakefulness-promoting agent that is not a controlled substance is necessary, per the prescriber.

2. Cataplexy Treatment in Patients with Narcolepsy. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has tried one of the following treatments: a tricyclic antidepressant, a selective serotonin reuptake inhibitor (SSRI), or venlafaxine; AND
  Note: Examples of tricyclic antidepressants include amitriptyline, desipramine, and imipramine. Examples of SSRIs include fluoxetine, sertraline, and paroxetine.
- **C)** Patient has been evaluated using polysomnography and a multiple sleep latency test (MSLT); AND
- **D)** Diagnosis of narcolepsy has been confirmed, according to the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Wakix is not recommended in the following situations:

274. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/02/2019
Selected Revision	Criteria stating that "the patient is ≥ 18 years of age" was added to the approval condition of **Narcolepsy**. Added "Excessive Daytime Sleepiness Associated with" to the approval criteria for narcolepsy and also added a requirement that narcolepsy has been confirmed with polysomnography and a multiple sleep latency test (MSLT).	03/25/2020
Early Annual Revision	For the approval condition of **Excessive Daytime Sleepiness Associated with Narcolepsy**, the criterion of "Narcolepsy has been confirmed with polysomnography and a multiple sleep latency test (MSLT)" was split into two criteria: "Patient has been evaluated using polysomnography and a multiple sleep latency test (MSLT)" and "Diagnosis of narcolepsy has been confirmed, according to the prescriber".	09/09/2020
Selected Revision	**Cataplexy Treatment in Patients with Narcolepsy**: Coverage criteria were added for this new indication.	10/28/2020

PRIOR AUTHORIZATION POLICY

POLICY: Weight Loss Drugs Prior Authorization Policy

- Adipex-P® (phentermine hydrochloride capsules and tablets – Teva, generics)
- benzphetamine hydrochloride tablets (generics only)
- Contrave® (naltrexone HCl/buproprion HCl extended-release tablets – Orexigen Therapeutics)
- diethylpropion hydrochloride immediate-release and controlled-release tablets (generics only)
- Lomaira™ (phentermine hydrochloride tablets – KVK-Tech)
- phendimetrazine tartrate tablets (generics only)
- phentermine hydrochloride orally disintegrating tablets (generics only)
- Regimex (benzphetamine 25 mg tablets – WraSer Pharmaceuticals, generics – obsolete 1/15/2019)
- Saxenda® (liraglutide [rDNA] injection – NovoNordisk)
- Qsymia™ (phentermine and topiramate extended-release capsules – Vivus, Inc.)
- Xenical® (orlistat 120 mg capsules − Roche)

REVIEW DATE 11/18/2020; selected revisions 01/20/2021; selected revision 02/10/2020

OVERVIEW

The appetite suppressant products vary slightly in the wording of their FDA-approved indications.

- **Benzphetamine**, **diethylpropion**, and **phendimetrazine** are indicated for the management of exogenous obesity as a short-term adjunct (a few weeks) to a regimen of weight reduction based on caloric restriction in patients with an initial body mass index (BMI) of ≥ 30 kg/m^2 who have not responded to a weight reducing regimen (diet and/or exercise) alone.[5-7,31]
- **Phentermine** hydrochloride is indicated for short-term (a few weeks) adjunctive therapy in a regimen of weight reduction based on exercise, behavioral modification and caloric restriction in the management of exogenous obesity in those with an initial BMI ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 when other risk factors are present (e.g., controlled hypertension, diabetes mellitus, or dyslipidemia).[8-9,30]
- **Qsymia** and **Contrave** are indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of ≥ 30 kg/m^2 (obese), or ≥ 27 kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes).[10,26]
- **Saxenda** is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in:
  - Adult patients with an initial BMI ≥ 30 kg/m^2 (obese), or ≥ 27 kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes),
  - Pediatric patients ≥ 12 years of age with body weight > 60 kg and an initial BMI corresponding to 30 kg/m^2 for adults (obese) by international cutoffs.[27]
- **Xenical** is indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet in patients with an initial body mass index ≥ 30 kg/m^2, or ≥ 27 kg/m^2 in the presence of at least one weight-related comorbidity (e.g., hypertension, diabetes, dyslipidemia), and to reduce the risk for weight gain after prior weight loss.[11]

This policy is limited to prescription medications that are indicated to promote weight loss in obese patients. Obesity in adults is defined as a body mass index (BMI) of ≥ 30 kg/m^2; a BMI of 25 to 29.9 kg/m^2 is termed overweight.[1] The combined prevalence of obesity and overweight is estimated at > 64% of US adults; 4.7% of adults have a BMI ≥ 40 kg/m^2. In the US, an estimated 300,000 adult deaths per year are due to obesity-related causes. With the increase in obesity, treatments for obesity have increased in number and are more commonly used. Diet therapy with a low calorie diet, increased physical activity, and behavioral modification are the mainstays of treatment of overweight and obese adults. Such a regimen should be maintained for at least 6 months before considering pharmacotherapy. The rationale for adding drug therapy to these regimens in selected adults is that a more successful weight loss and maintenance may result.[2-3] Weight loss goals should be individually determined and these goals may include not just weight loss but other parameters, such as improved glucose metabolism, lipid levels, and blood pressure.[1]

Drugs that are indicated for weight loss either: 1) decrease food intake by decreasing appetite or increasing satiety (appetite suppressant, anorectic), or 2) decrease nutrient absorption.[4] The appetite suppressants increase the availability of anorexigenic neurotransmitters (norepinephrine, serotonin, dopamine, or some combination of these) in the central nervous system (CNS). Orlistat acts by inhibiting the absorption of dietary fats and is not an appetite suppressant.[11]

Contrave

The recommended maintenance dose of Contrave is achieved at Week 4.[26] Response to therapy should be evaluated after 12 weeks at the maintenance dosage (Week 16, if dosed according to the prescribing information). If a patient has not lost ≥ 5% of baseline body weight, discontinue Contrave, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

Qsymia

Response to therapy should be evaluated by Week 12.[10] If a patient has not lost ≥ 3% of baseline body weight, discontinue Qsymia or escalate the dose. If a patient has not lost ≥ 5% of baseline body weight after an additional 12 weeks of treatment on the escalated dose, discontinue Qsymia as directed as it is unlikely the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

Saxenda

The change in body weight with Saxenda should be evaluated 16 weeks after initiating Saxenda.[27] If the patient has not lost ≥ 4% of baseline body weight, Saxenda should be discontinued because it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

Guidelines

The Endocrine Society published a clinical practice guideline (2015) for the pharmacological management of obesity.[28] The guidelines recommend that pharmacotherapy be employed for patients with BMI ≥ 27 kg/m^2 with comorbidity or BMI > 30 kg/m^2 as adjuncts to behavioral modification to reduce food intake and increase physical activity when possible. The Society states that patients who have a history of being unable to successfully lose and maintain weight and who meet label indications are candidates for weight-loss medication. Safety and efficacy is recommended to be assessed monthly for the first three months, and then at least every 3 months in all patients prescribed medications for weight loss. If a patient has an adequate response to weight loss medication (weight loss ≥ 5% at 3 months), medication is recommended to be continued. If deemed to be ineffective (weight loss < 5% at 3 months) or if there are safety or tolerability issues at any time, it is recommended that medication be discontinued and alternative medications or referral for alternative treatment approaches be considered.

Although the noradrenergic weight loss medications are only labeled for short-term use, the Endocrine Society (2015) notes that off-label, long-term prescribing of phentermine is reasonable for most patients, as long as the patient has been informed that other medications for weight loss are FDA-approved for long-term use.[28] According to prescribing information, safety and efficacy have not been established for diethylpropion and phentermine (hydrochloride or resin) in children younger than 16 years,[6,8,9,30] and for benzphetamine, phendimetrazine and Xenical in children < 12 years of age.[5,7,11,31] However, the Endocrine Society has established guidelines for use of Xenical in pediatric patients.[16] Benzphetamine, diethylpropion, phendimetrazine and phentermine are not included in these guidelines.

The American Association of Clinical Endocrinology (AACE)/American College of Endocrinology (ACE) guidelines for medical care of patients with obesity (2016) recommend pharmacotherapy for overweight and obese patients only as an adjunct to lifestyle therapy.[29] Pharmacotherapy should be offered to patients who are obese when the potential benefits outweigh the risks, for the chronic treatment of obesity. Short-term (3 to 6 months) use of weight-loss medications has not been demonstrated to produce longer-term health benefits and cannot be generally recommended.

Guidelines in Pediatric Obesity

A 2017 Endocrine Society clinical practice guideline on pediatric obesity recommends pharmacotherapy in combination with lifestyle modification be considered in obese children or adolescents only after failure of a formal program of intensive lifestyle [dietary, physical activity and behavioral] modification to limit weight gain or to ameliorate comorbidities.[16] The Endocrine Society recommends pharmacotherapy in overweight children and adolescents < 16 years only in the context of a clinical trial. Pharmacotherapy

should be provided only by clinicians who are experienced in the use of antiobesity agents and aware of the potential for adverse events. These guidelines recommend limited use of pharmacotherapy because pediatric obesity should be managed preferably as a serious lifestyle condition with important lifelong consequences.

The Endocrine Society defines overweight as BMI in at least the 85th percentile but less than the 95th percentile, and obesity as BMI in at least the 95th percentile for age and sex against routine endocrine studies, unless the height velocity is attenuated or inappropriate for the family background or stage of puberty.[16] The Centers for Disease Control (CDC) derived normative percentiles are recommended as the appropriate method for determining the BMI in children.[17-18]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of benzphetamine, diethylpropion, phendimetrazine tartrate, phentermine hydrochloride, Qsymia, Contrave, Saxenda, and Xenical. All approvals are provided for the durations noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Prior Authorization and prescription benefit coverage is not recommended for Alli.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of benzphetamine (including Regimax 25 mg tablets [generics]), diethylpropion, phendimetrazine tartrate, or phentermine hydrochloride is recommended in those who meet all of the following criteria:

FDA-Approved Indications

4. Weight Loss in Patients ≥ 16 Years of Age. Note: For individuals who have not completed the initial 3 months of therapy, criterion (1A) must be met (do not use continuation criteria if the initial 3 months were not completed).

A) Initial Therapy. Approve for 3 months if the patient meets all of the following criteria (i, ii, and iii):

- **i.** Patient currently has a body mass index (BMI) ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 for those with comorbidities besides obesity (Appendix A contains a BMI chart); AND
  Note: Examples of comorbidities include diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea.
- **ii.** Patient has engaged in a trial of behavioral modification and dietary restriction for at least 3 months and has failed to achieve the desired weight loss; AND
- **iii.** Patient is currently engaged in behavioral modification and on a reduced calorie diet.

B) Patient is Continuing Therapy. Approve for 12 months if the patient meets all of the following criteria (i, ii, and iii):

- **i.** Patient had an initial BMI ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 for those with comorbidities besides obesity: AND
  Note: Examples of comorbidities include diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea.
- **ii.** Patient is currently engaged in behavioral modification and on a reduced calorie diet; AND
- **iii.** Patient has lost ≥ 5% of baseline body weight.

II. Coverage of Contrave is recommended in those who meet all of the following criteria:

FDA-Approved Indications

1. **Weight Loss in Patients ≥ 18 Years of Age.** Note: For individuals who have not completed the initial 4 months of therapy, criterion (1A) must be met (do not use continuation criteria if the initial 4 months were not completed).
   - **A)** Initial Therapy. Approve for 4 months if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient currently has a body mass index (BMI) ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 for those with comorbidities besides obesity (Appendix A contains a BMI chart); AND
       Note: Examples of comorbidities include diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea.
     - **ii.** Patient has engaged in a trial of behavioral modification and dietary restriction for at least 3 months and has failed to achieve the desired weight loss; AND
     - **iii.** Patient is currently engaged in behavioral modification and on a reduced calorie diet.
   - **B)** Patient is Continuing Therapy. Approve for 12 months if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient had an initial BMI ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 for those with comorbidities besides obesity: AND
       Note: Examples of comorbidities include diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea.
     - **ii.** Patient is currently engaged in behavioral modification and on a reduced calorie diet; AND
     - **iii.** Patient has lost ≥ 5% of baseline body weight.

III. Coverage of Qsymia is recommended in those who meet all of the following criteria:

FDA-Approved Indications

1. **Weight Loss in Patients ≥ 18 Years of Age.** Note: For individuals who have not completed the initial 6 months of therapy, criterion (1A) must be met (do not use continuation criteria if the initial 6 months were not completed).
   - **A)** Initial Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient currently has a BMI ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 for those with comorbidities besides obesity (Appendix A contains a BMI chart); AND
       Note: Examples of comorbidities include diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea.
     - **ii.** Patient has engaged in a trial of behavioral modification and dietary restriction for at least 3 months and has failed to achieve the desired weight loss; AND
     - **iii.** Patient is currently engaged in behavioral modification and on a reduced calorie diet.
   - **B)** Patient is Continuing Therapy. Approve for 12 months if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient had an initial BMI ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 for those with comorbidities besides obesity; AND
       Note: Examples of comorbidities include diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea.
     - **ii.** Patient is currently engaged in behavioral modification and on a reduced calorie diet; AND
     - **iii.** Patient has lost ≥ 5% of baseline body weight.

IV. Coverage of Saxenda is recommended in those who meet all of the following criteria:

1. **Weight Loss in Patients ≥ 18 years of Age.** Note: For individuals who have not completed the initial 4 months of therapy, criterion (1A) must be met (do not use continuation criteria if the initial 4 months were not completed).
   - **A)** Initial Therapy. Approve for 4 months if the patients meets the following criteria (i, ii, and iii):
     - **i.** Patient currently has a BMI ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 for those with comorbidities besides obesity (Appendix A contains a BMI chart); AND
       Note: Examples of comorbidities include diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea.
     - **ii.** Patient has engaged in a trial of behavioral modification and dietary restriction for at least 3 months and has failed to achieve the desired weight loss; AND
     - **iii.** Patient is currently engaged in behavioral modification and on a reduced calorie diet.
   - **B)** Patient is Continuing Therapy. Approve for 12 months if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient had an initial BMI ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 for those with comorbidities besides obesity; AND
       Note: Examples of comorbidities include diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea.
     - **ii.** Patient is currently engaged in behavioral modification and on a reduced calorie diet; AND
     - **iii.** Patient has lost ≥ 4% of baseline body weight.

2. **Weight Loss in Patients Aged ≥ 12 to < 18 Years.** Note: For individuals who have not completed the initial 4 months of therapy, criterion (2A) must be met (do not use continuation criteria if the initial 4 months were not completed).
   - **A)** Initial Therapy. Approve for 4 months if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient currently has a BMI of ≥ 95th percentile for age and sex, or in ≥ 85th percentile but < 95th percentile for age and sex and has at least one comorbidity (type 2 diabetes mellitus, cardiovascular disease [CVD]) or has a strong family history of type 2 diabetes or premature CVD; AND
       Note: Premature cardiovascular disease is defined as cardiovascular disease occurring in a male < 55 years of age or in a female < 65 years of age.
     - **ii.** Patient has engaged in a trial of behavioral modification and dietary restriction for at least 4 months and has failed to limit weight gain or to modify comorbidities; AND
     - **iii.** Patient is currently engaged in behavioral modification and on a reduced calorie diet.
   - **B)** Patient is Continuing Therapy. Approve for 12 months if the patient meets the following criteria (i, ii, iii, and iv):
     - **i.** Patient had an initial BMI of ≥ 95th percentile for age and sex, or ≥ 85th percentile but < 95th percentile for age and sex and has at least one comorbidity (type 2 diabetes or CVD) or strong family history of type 2 diabetes or premature CVD; AND
       Note: Premature cardiovascular disease is defined as cardiovascular disease occurring in a male < 55 years of age or in a female < 65 years of age.
     - **ii.** Patient is currently engaged in behavioral modification and on a reduced calorie diet; AND
     - **iii.** Patient has had a reduction in BMI of ≥ 1% from baseline; AND
     - **iv.** Patient currently has a BMI > 85th percentile.

V. Coverage of Xenical is recommended in those who meet all of the following criteria:

FDA-Approved Indications

1. **Weight Loss in Patients ≥ 18 Years of Age**. Note: For individuals who have not completed the initial 3 months of therapy, criterion (1A) must be met (do not use continuation criteria if the initial 3 months were not completed).
   - **A)** Initial Therapy. Approve for 3 months if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient meets ONE of the following (a or b):
       - **a)** Patient currently has a BMI ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 for those with comorbidities besides obesity (Appendix A contains a BMI chart); OR
         Note: Examples of comorbidities include diabetes, dyslipidemia, hypertension, coronary heart disease, sleep apnea.
       - **b)** Patient had an initial BMI ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 for those with comorbidities besides obesity if maintaining weight loss after using a low calorie diet; AND
         Note: Examples of comorbidities include diabetes, dyslipidemia, hypertension, coronary heart disease, sleep apnea.
     - **ii.** Patient has engaged in a trial of behavioral modification and dietary restriction for at least 3 months and has failed to achieve the desired weight loss; AND
     - **iii.** Patient is currently engaged in behavioral modification and on a reduced calorie diet.
   - **B)** Patient is Continuing Therapy. Approve for 12 months if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient had an initial BMI ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 for those with comorbidities besides obesity: AND
       Note: Examples of comorbidities include diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea.
     - **ii.** Patient is currently engaged in behavioral modification and on a reduced calorie diet; AND
     - **iii.** Patient has lost ≥ 5% of baseline body weight.

2. **Weight Loss in Patients Aged ≥ 12 to < 18 Years.** Note: For individuals who have not completed the initial 3 months of therapy, criterion (2A) must be met (do not use continuation criteria if the initial 3 months were not completed).
   - **A)** Initial Therapy. Approve for 3 months if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient currently has a BMI of ≥ 95th percentile for age and sex, or in ≥ 85th percentile but < 95th percentile for age and sex and has at least one comorbidity (type 2 diabetes mellitus, cardiovascular disease [CVD]) or has a strong family history of type 2 diabetes or premature CVD; AND
       Note: Premature cardiovascular disease is defined as cardiovascular disease occurring in a male < 55 years of age or in a female < 65 years of age.
     - **ii.** Patient has engaged in a trial of behavioral modification and dietary restriction for at least 3 months and has failed to limit weight gain or to modify comorbidities; AND
     - **iii.** Patient is currently engaged in behavioral modification and on a reduced calorie diet.
   - **B)** Patient is Continuing Therapy. Approve for 12 months if the patient meets the following criteria (i, ii, iii, and iv):
     - **i.** Patient had an initial BMI of ≥ 95th percentile for age and sex, or ≥ 85th percentile but < 95th percentile for age and sex and has at least one comorbidity (type 2 diabetes or CVD) or strong family history of type 2 diabetes or premature CVD; AND
       Note: Premature cardiovascular disease is defined as cardiovascular disease occurring in a male < 55 years of age or in a female < 65 years of age.
     - **ii.** Patient is currently engaged in behavioral modification and on a reduced calorie diet; AND
     - **iii.** Patient's current BMI percentile has decreased for age and weight (taking into account that the patient is increasing in height and will have a different normative BMI from when Xenical was started); AND

iv. Patient currently has a BMI > 85th percentile.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of benzphetamine, diethylpropion, phendimetrazine tartrate, phentermine hydrochloride, Qsymia, Contrave, Saxenda, and Xenical is not recommended in the following situations:

1. **Combination Appetite Suppressant Therapy**. Appetite suppressants (benzphetamine, diethylpropion, phendimetrazine tartrate, phentermine hydrochloride or resin, Qsymia, Contrave, Saxenda) are indicated *only* as monotherapy and should not be used in combination with other appetite suppressant drugs.[5-10,26-27,30-31] A 12-week, pilot study assessed the addition of phentermine to Saxenda following 1 year of Saxenda treatment.[33] A total of 45 patients were randomized to Saxenda plus phentermine or Saxenda plus placebo. At 12 weeks, the patients in the Saxenda plus phentermine group had numerically, but not statistically, larger reduction in weight compared with the Saxenda plus placebo group (1.6% vs. 0.1%, respectively, P = 0.073). This study was of inadequate size and duration to assess for long-term safety and efficacy, particularly in regard to cardiovascular outcomes.

2. **Simultaneous Use of Xenical with Any of the Following: benzphetamine, diethylpropion, phendimetrazine tartrate, or phentermine hydrochloride or resin, Contrave, Saxenda or Qsymia.** Limited information from published well-controlled studies is available on the combination use of these drugs. Using weight loss drugs one at a time and starting with the lowest effective doses can decrease the chance of adverse effects.[2] Unproven combination therapy is not recommended.[4]

3. **Treatment of Hyperlipidemia in Non-Obese Patients**. Short-term use of Xenical has slightly decreased total and low density lipoprotein (LDL) cholesterol in patients with increased total and LDL cholesterol levels and normal triglyceride levels who were not obese (BMI 19 to 28.7 kg/m^2).[20] Triglycerides were unchanged and high density lipoprotein (HDL) cholesterol tended to decrease. Although not directly compared with other drugs, Xenical's effects on total and LDL cholesterol were less than those observed with hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (HMGs) and low dose cholestyramine.

4. **Treatment of Binge-Eating Disorder in Non-Obese Patients (BMI < 30 kg/m^2 or < 27 kg/m^2 for Those with Risk Factors).** In a short term (12 or 24 week) placebo-controlled trial in obese patients (BMI ≥ 30 kg/m^2) with binge eating disorder, Xenical has been effective in producing weight loss.[21-22] In an open-label study, 10 patients with binge eating disorder were treated with Qsymia.[34] Nine of the patients were obesity and one was overweight. After 12 weeks of treatment, the patients on average lost 4.9 kg of body weight. Patients with binge-eating disorder are usually obese and should be reviewed for weight loss therapy using the criteria in the section above.

5. **Prevention of Diabetes in Patients with BMI < 30 kg/m^2.** In a large (n = 3,305) 4-year study, Xenical, in addition to lifestyle changes, led to a 37% risk reduction in the development of type 2 diabetes in obese (BMI ≥ 30 kg/m^2) patients compared with placebo.[13] However, those most affected had impaired glucose tolerance at baseline and these patients achieved a more pronounced weight reduction. Qsymia in addition to lifestyle modification reduced the progression to type 2 diabetes in overweight/obese patients (BMI 27 to 45 kg/m^2) plus at least two weight-related comorbidities with pre-existing prediabetes and/or metabolic syndrome in a 108-week study compared with placebo (n = 475). However, the magnitude of effect for prevention of type 2 diabetes was related to the degree of weight loss achieved in this sub-analysis. Such patients should be evaluated based on overweight or obesity using the appropriate criteria above.

6. **Nonalcoholic Fatty Liver Disease.** In a single-center trial, 52 patients with nonalcoholic fatty liver disease were randomized to Xenical 120 mg three times daily or placebo.[23] Mean BMI was 33 kg/m^2. All patients were in a behavioral weight loss program. Forty-four patients completed 6 months and their results were analyzed. Patients were not well-matched for baseline characteristics (e.g., BMI, waist circumference, glucose and insulin levels were significantly different between groups at baseline). The authors concluded that Xenical improves serum alanine aminotransferase (ALT) and steatosis on ultrasound in these patients beyond its effect on weight reduction. An additional 24 week study, compared Xenical (n = 68) with conventional treatment (n = 102) in patients with nonalcoholic fatty liver disease and a BMI of ≥ 25 kg/m^2 using magnetic resonance imaging-derived proton density fat fraction.[35] After 24 weeks of treatment, patients treated with Xenical had significantly greater reduction in total liver fat compared with the conventional treatment group (-5.45% vs. -1.96%, P < 0.001). In addition, steatosis improved in more patients treated with Xenical compared with the conventional treatment arm (57.3% vs. 23.5%, p < 0.001). Long-term, well-designed trials in a large number of patients are needed to determine if Xenical has a place in therapy for nonalcoholic fatty liver disease. In a small, randomized trial, Saxenda was compared with lifestyle modification in obese patients with nonalcoholic fatty liver disease.[36] After 26 weeks, similar reductions in weight (-3.3 kg vs. -3.0 kg), liver fat fraction (-8.1% vs. -7.0%), alanine aminotransferase (-39 U/L vs. -26 U/L), and caspase-cleaved cytokeratin-18 (-206 U/L vs. -130 U/L) occurred in the lifestyle modification and Saxenda groups, respectively. However, after discontinuing Saxenda, patients regained weight and liver fat fraction at week 52 while patients in the lifestyle modification group maintained the improvements in weight and liver fat fraction. There is very little good quality evidence to support or refute the use of weight reduction as a treatment for nonalcoholic fatty liver disease.[24]

7. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Brand Bontril PDM and Suprenza removed from policy (obsolete for > 3 years).	10/30/2019
Selected Revision	Removed Belviq and Belviq XR from policy after both were pulled from the market.	3/11/2020
Annual Revision	No criteria changes.	11/18/2020
Update	12/07/2020: Criteria for benzphetamine, diethylpropion, phendimetrazine, phentermine, Contrave, Qsymia, Saxenda, and Xenical in Adults > 18 years of age were revised from: BMI ≥ 27 kg/m^2 for those with "risk factors" besides obesity, TO: BMI ≥ 27 kg/m^2 for those with "comorbidities" besides obesity. Examples in the Note were changed from "risk factors" to "comorbidities".	NA
Selected Revision	**Saxenda**: Added criteria for the use of Saxenda in pediatric patients ≥ 12 and < 18 years of age.	01/20/2021

	Xenical: Criteria for adults was revised by changing risk factors to comorbidities. Criteria for pediatric patients was revised by removing "severe" from criteria – has at least one "severe" comorbidity.	
Selected Revision	**Saxenda, Weight Loss in Patients Aged ≥ 12 to < 18 Years**: Removed "premature" from comorbidities in Initial Therapy and Patient is Continuing Therapy criteria. Now reads as follows: ≥ 85th percentile but < 95th percentile for age and sex and has at least one comorbidity (type 2 diabetes, ~~premature~~ cardiovascular disease). Added Note: Premature cardiovascular disease is defined as cardiovascular disease occurring in males < 55 years of age or in females < 65 years of age. **Xenical, Weight Loss in Patients Aged ≥ 12 to < 18 Years**: Removed "premature" from comorbidities in Initial Therapy and Patient is Continuing Therapy criteria. Now reads as follows: ≥ 85th percentile but < 95th percentile for age and sex and has at least one comorbidity (type 2 diabetes, ~~premature~~ cardiovascular disease). Added Note: Premature cardiovascular disease is defined as cardiovascular disease occurring in males < 55 years of age or in females < 65 years of age.	02/10/2021

BMI – Body mass index.

APPENDIX A

Below is a chart of BMI based on various heights and weights.[2] To use the table, find the appropriate height in the far left column, and move across the row to the given weight; the number at the top of the column is the BMI. For example, a patient who is 5 feet 6 inches in height and weighs 192 pounds has a BMI of 31 kg/m^2.

BMI can also be calculated using the following formula: BMI equals body weight in kilograms divided by height meters squared (m^2), i.e., BMI = kg/m^2.

Body Mass Index

BMI, kg/m^2	25	26	27	28	29	30	31	32	33	34	35	40
Height (feet, inches)	Weight (pounds)											
4'10"	119	124	129	134	138	143	148	153	158	162	167	191
4'11"	124	128	133	138	143	148	153	158	163	168	173	198
5'0"	128	133	138	143	148	153	158	163	168	174	179	204
5'1"	132	137	143	148	153	158	164	169	174	180	185	211
5'2"	136	142	147	153	158	164	169	175	180	186	191	218
5'3"	141	146	152	158	163	169	175	180	186	191	197	225
5'4"	145	151	157	163	169	174	180	186	192	197	204	232
5'5"	150	156	162	168	174	180	186	192	198	204	210	240
5'6"	155	161	167	173	179	186	192	198	204	210	216	247
5'7"	159	166	172	178	185	191	198	204	211	217	223	255
5'8"	164	171	177	184	190	197	203	210	216	223	230	262
5'9"	169	176	182	189	196	203	209	216	223	230	236	270
5'10"	174	181	188	195	202	209	216	222	229	236	243	278
5'11"	179	186	193	200	208	215	222	229	236	243	250	286
6'0"	184	191	199	206	213	221	228	235	242	250	258	294
6'1"	189	197	204	212	219	227	235	242	250	257	265	302
6'2"	194	202	210	218	225	233	241	249	256	264	272	311
6'3"	200	208	216	224	232	240	248	256	264	272	279	319
6"4"	205	213	221	230	238	246	254	263	271	279	287	328

PRIOR AUTHORIZATION POLICY

POLICY: Xiaflex Prior Authorization Policy

- Xiaflex® (collagenase clostridium histolyticum for intralesional injection – Endo Pharmaceuticals)

REVIEW DATE: 02/03/2021

OVERVIEW

Xiaflex, a combination of bacterial collagenases, is indicated for the following:

- **Dupuytren's contracture** with a palpable cord in adults.
- **Peyronie's disease** in adult men with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.[1]

Disease Overview

Dupuytren's contracture is a disorder of the palmar and digital fascia of the hand.[2] Abnormal deposition of collagen initially causes nodules in the palm of the hand, which may thicken and lead to formation of cords. As the disease progresses, the cords gradually contract, leading to flexion deformities of the fingers. Joint contractures are typically painless but are associated with significant functional impairment. The exact etiology of Dupuytren's contracture is unknown, although a number of risk factors have been reportedly associated with the condition, including alcohol,

smoking, diabetes, epilepsy, thyroid disorders, and trauma. Prevalence varies widely by age and geographical location but is most common among Caucasian males greater than 50 years of age. Surgical intervention, either by open partial fasciectomy or percutaneous needle fasciotomy, is the mainstay of therapy for severe cases. However, surgery may be associated with complications including neurovascular injury or hematoma, and recurrence after surgery is common. In clinical studies of Dupuytren's contracture, patients were eligible to participate if they had a finger contraction of 20 degrees to 100 degrees in a metacarpophalangeal joint or 20 degrees to 80 degrees in a proximal interphalangeal joint.[1]

Peyronie's disease is an acquired penile abnormality caused by fibrosis of the tunica albuginea, which may lead to pain, deformity, erectile dysfunction, and/or distress.[3] It is thought that repeated minor trauma to the penis initiates a cascade involving extravascular protein deposition, fibrin trapping, and overexpression of cytokines, leading to collagen changes characteristic of the condition. Males around 50 years of age are most commonly affected. Peyronie's disease has a variable course; for most patients, pain will resolve over time without intervention, but curvature deformities are less likely to resolve without treatment. Intralesional therapy with Xiaflex may be used to treat curvature associated with Peyronie's disease and is supported by American Urological Association guidelines (2015).

Dosing Considerations

For treatment of Dupuytren's contracture, the dose of Xiaflex is 0.58 mg per injection into a palpable cord with a contracture of an metacarpophalangeal or proximal interphalangeal joint.[1] Two palpable cords affecting two joints or one palpable cord affecting two joints in the same finger may be injected per treatment visit. Injections may be administered up to three times per cord at approximately 4-week intervals.

For treatment of Peyronie's disease, one treatment course consistent of four cycles.[1] Each cycle consists of two Xiaflex injection procedures (1 to 3 days apart). Up to four cycles of Xiaflex may be administered, given at approximately 6-week intervals. The safety of more than one treatment course (8 total injections) is unknown.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Xiaflex. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Xiaflex, approval requires it to be administered by a healthcare provider with expertise in the condition being treated.

Prior authorization and prescription benefit coverage are not recommended for Xiaflex for cosmetic uses.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xiaflex is recommended in those who meet the following criteria:

FDA-Approved Indications

7. **Dupuytren's Contracture.** Approve Xiaflex for 3 months if the patient meets all of the following criteria (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** At baseline (prior to initial injection of Xiaflex), the patient had contracture of a metacarpophalangeal or proximal interphalangeal joint of at least 20 degrees; AND
   - **C)** Patient will not be treated with more than a total of three injections (maximum) per affected cord; AND
   - **D)** Xiaflex is administered by a healthcare provider experienced in injection procedures of the hand and in the treatment of Dupuytren's contracture.

8. **Peyronie's Disease.** Approve Xiaflex for 6 months if the patient meets all of the following criteria (A, B, C, and D):

A) Patient is ≥18 years of age; AND
B) Patient meets one of the following (i or ii):
  i. At baseline (prior to use of Xiaflex), the patient has a penile curvature deformity of at least 30 degrees; OR
  ii. In a patient who has received prior treatment with Xiaflex, the patient has a penile curvature deformity of at least 15 degrees; AND
C) Patient has not previously been treated with a complete course (8 injections) of Xiaflex for Peyronie's disease; AND
D) Xiaflex is being administered by a healthcare provider experienced in the treatment of male urological diseases.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xiaflex is not recommended in the following situations:

275. Cosmetic Uses (e.g., cellulite of buttocks). Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical pharmacy benefit.

276. Retreatment (i.e., treatment beyond three injections per affected cord for those with Dupuytren's Contracture or beyond eight injections for Peyronie's Disease). For Dupuytren's contracture, injections and finger extension procedures may be administered up to three times per cord.[1] However, this does not limit treatment of additional cords. For Peyronie's disease, the safety of more than one treatment course (8 injections) is unknown.

277. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/30/2019
Annual Revision	No criteria changes.	01/29/2020
Annual Revision	No criteria changes.	02/03/2021

PRIOR AUTHORIZATION POLICY WITH STEP THERAPY

POLICY: Xyrem/Xywav Prior Authorization Policy with Step Therapy
- Xyrem® (sodium oxybate oral solution – Jazz Pharmaceuticals)
- Xywav™ (calcium, magnesium, potassium, and sodium oxybates oral solution – Jazz Pharmaceuticals)

REVIEW DATE: 10/07/2020

OVERVIEW

Xyrem and Xywav, central nervous system (CNS) depressants, are indicated for the following uses:[1,2]

- **Cataplexy treatment in patients with narcolepsy**, in patients ≥ 7 years of age.
- **Excessive daytime sleepiness in narcolepsy**, in patients ≥ 7 years of age.

Xyrem and Xywav have the same oxybate concentration; Xywav includes a mix of calcium, magnesium, potassium and sodium cations, while Xyrem includes only sodium cations.[1,2] Dosing and administration of Xyrem and Xywav are the same.

Xyrem labeling includes a Warning with regard to patients sensitive to high sodium intake which states that Xyrem has a high salt content.[1] In patients sensitive to salt intake (e.g., those with heart failure, hypertension, or renal impairment), consider the amount of daily sodium intake in each dose of Xyrem. According to the manufacturer, Xywav has 92% less sodium (approximately 1,000mg to 1,500mg less per night) than Xyrem.[2]

Two specialized tests, which can be performed in a sleep disorders clinic, are required to establish a diagnosis of narcolepsy.[3] Polysomnography is an overnight recording of brain and muscle activity, breathing, and eye movements. The multiple sleep latency test (MSLT) assesses daytime sleepiness by measuring how quickly a person falls asleep and whether they enter rapid eye movement (REM) sleep. Polysomnography is routinely indicated for the diagnosis of sleep-related breathing disorders; for continuous positive airway pressure titration in patients with sleep-related breathing disorders; with a MSLT in the evaluation of suspected narcolepsy; and in certain atypical or unusual parasomnias.[4] The MSLT is indicated as part of the evaluation of patients with suspected narcolepsy to confirm the diagnosis. Most patients with narcolepsy have objective evidence of hypersomnia as determined by a mean sleep latency < 5 minutes. In studies, the presence of two or more sleep-onset REM episodes (SOREMPs) was associated with a sensitivity of 0.78 and a specificity of 0.93 for the diagnosis of narcolepsy. SOREMPs do not occur exclusively in patients with narcolepsy, and thus it is important to rule out or treat other sleep disorders before evaluating SOREMPs in the diagnosis of narcolepsy. For this reason, polysomnography and a MSLT performed on the day after the polysomnographic evaluation are routinely indicated in the evaluation of suspected narcolepsy.

Guidelines

Guidelines for the treatment of narcolepsy and for cataplexy due to narcolepsy are dated and do not include Xywav.[5,6] The American Academy of Sleep Medicine (AASM) practice parameters for the treatment of narcolepsy and other hypersomnias of central origin (2007) list Xyrem as effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy (*Standard*) and modafinil as an effective for treatment of daytime sleepiness due to narcolepsy (*Standard*). Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are considered effective for the treatment of daytime sleepiness due to narcolepsy (*Guideline*). Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and venlafaxine may be effective for the treatment of cataplexy (*Guideline*). Selegiline may be an effective treatment for cataplexy and daytime sleepiness (*Option*). *Standard* recommendations are considered to be generally accepted patient-care strategies that reflect a high degree of clinical certainty based on Level I evidence or overwhelming Level II evidence. *Guideline* recommendations are considered to be patient-care strategies that reflect a moderate degree of clinical certainty based on Level II evidence or a consensus of Level III evidence. *Option* recommendations are considered to be patient-care strategies that reflect uncertain clinical use based on inconclusive or conflicting evidence or conflicting expert opinion. At the time this practice parameter was written, published studies involving Nuvigil® (armodafinil tablets) were limited.

The European League Against Rheumatism (EULAR) issued updated evidence-based recommendations for the management of fibromyalgia (2016) stating that initial management should involve patient education and focus on nonpharmacological therapies.[7] In case of non-response, further therapies should be tailored to the specific needs of the individual and may involve psychological therapies (for mood disorders and

unhelpful coping strategies), pharmacotherapy (for severe pain or sleep disturbance) and/or a multimodal rehabilitation program (for severe disability). EULAR notes that the European Medicines Agency and the FDA refused approval of Xyrem for fibromyalgia because of safety concerns. EULAR's position on Xyrem for fibromyalgia is strongly against with 94% agreement.

Safety

Xyrem is the sodium salt of gamma hydroxybutyrate (GHB) and Xywav is a mixed salt formulation of GHB.[1,2] They are both Schedule III controlled substances. Abuse of GHB (a Schedule I controlled substance), either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. Because of the risks of CNS depression, abuse, and misuse, Xyrem and Xywav are available only through a restricted distribution program called the Xyrem/Xywav Success Program, using a centralized pharmacy. Healthcare professionals who prescribe Xyrem or Xywav and patients must enroll in the Xyrem/Xywav Success Program and must comply with the requirements to ensure the drug's safe use.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Xyrem and Xywav. Because Xyrem and Xywav have been associated with significant risks, including CNS and respiratory depression, and have the potential for abuse, misuse, and overdose, approval requires Xyrem and Xywav to be prescribed by a physician who specializes in the condition being treated. When clinically appropriate, patients are directed to try the Preferred Step 1 agent (Xyrem) prior to Xywav (Step 2). All approvals are provided for the duration noted below.

Automation: Grandfathering is not clinically necessary for Xyrem. Refer to the AUM reference guide for additional information.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Xyrem or Xywav is recommended in those who meet the following criteria:

FDA-Approved Indications

37. Cataplexy Treatment in Patients with Narcolepsy. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):

- **G)** Patient has tried one of the following treatments: a tricyclic antidepressant (TCA), a selective serotonin reuptake inhibitor (SSRI), or venlafaxine; AND
  Note: Examples of tricyclic antidepressants include amitriptyline, desipramine, and imipramine. Examples of SSRIs include fluoxetine, sertraline, and paroxetine.
- **H)** Patient has been evaluated using polysomnography and a multiple sleep latency test (MSLT); AND
- **I)** Diagnosis of narcolepsy has been confirmed, according to the prescriber; AND
- **J)** The medication has been prescribed by a sleep specialist physician or a neurologist; AND
- **K)** If the request is for Xywav, the patient must meet one of the following (i or ii):
  a. Patient has tried Xyrem and has experienced inadequate efficacy or significant intolerance according to the prescriber; OR
  b. According to the prescriber, the patient has a concomitant diagnosis of heart failure, hypertension, or renal impairment.

38. Excessive Daytime Sleepiness in Patients with Narcolepsy. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):

A) Patient has tried one of the following treatments: a central nervous system (CNS) stimulant, modafinil, or armodafinil; AND
Note: Examples of CNS stimulants include methylphenidate, dexmethylphenidate, and dextroamphetamine.
B) Patient has been evaluated using polysomnography and a multiple sleep latency test (MSLT); AND
C) Diagnosis of narcolepsy has been confirmed, according to the prescriber; AND
D) The medication has been prescribed by a sleep specialist physician or a neurologist; AND
E) If the request is for Xywav, the patient must meet one of the following (i or ii):
- **i.** Patient has tried Xyrem and has experienced inadequate efficacy or significant intolerance according to the prescriber; OR
- **ii.** According to the prescriber, the patient has a concomitant diagnosis of heart failure, hypertension, or renal impairment.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xyrem or Xywav is not recommended in the following situations:

28. Fibromyalgia. The effectiveness of Xyrem in fibromyalgia has been evaluated in clinical trials of varying size.[8-13] However, due to safety concerns, Xyrem is not recommended for approval for fibromyalgia at this time. Duloxetine, Lyrica® (pregabalin capsules and oral solution), and Savella® (milnacipran tablets) are indicated for the treatment of fibromyalgia.[14-16] Other recommended treatments include TCAs (i.e., amitriptyline), cyclobenzaprine, gabapentin, and SSRIs (i.e., fluoxetine, sertraline, paroxetine).[17]

29. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No change to criteria.	03/07/2018
Selected Revision	Change to criteria for Cataplexy Treatment in Patients with Narcolepsy: removed modafinil and Nuvigil from list of previous treatment options. Added requirement of sleep studies (polysomnography and a MSLT) to both approval conditions. Changed the required number of previous alternative CNS stimulants (e.g., methylphenidate, dexmethylphenidate, dextroamphetamine), modafinil, or armodafinil from one to two for the criterion for Excessive Daytime Sleepiness in Patients with Narcolepsy.	07/25/2018
Annual Revision	No change to criteria.	03/20/2019
Annual Revision	No change to criteria.	03/25/2020
Selected Revision	For the criterion of Excessive Daytime Sleepiness in Patients with Narcolepsy, the required number of previous alternative CNS stimulants, modafinil, or armodafinil was changed from two to one, and the examples of CNS stimulants were moved to a note. For the criterion of Cataplexy Treatment in Patients with Narcolepsy, examples of tricyclic antidepressants and SSRIs were moved to a note.	06/24/2020
Early Annual Revision	Addition of Xywav to the policy as a Step 2 product, requiring a trial of Xyrem (Step 1 product) first, unless the patient has a concomitant diagnosis of heart failure, hypertension, or renal impairment. **Cataplexy Treatment in Patients with Narcolepsy** and **Excessive Daytime Sleepiness Associated with Narcolepsy:** The criterion of "Narcolepsy has been confirmed with polysomnography and a multiple sleep latency test (MSLT)" was split into two criteria: "Patient has been evaluated using polysomnography and a multiple sleep latency test (MSLT)" and "Diagnosis of narcolepsy has been confirmed, according to the prescriber".	10/07/2020

CNS – Central nervous system; SSRIs – Selective serotonin reuptake inhibitors.

PRIOR AUTHORIZATION POLICY

POLICY: Zokinvy Prior Authorization Policy
- Zokinvy™ (lonafarnib capsules – Eiger Biopharmaceuticals)

REVIEW DATE: 01/20/2021

OVERVIEW

Zokinvy, a protein farnesyltransferase inhibitor, is indicated in patients ≥ 12 months of age with a body surface area ≥ 0.39 m^2 for the following conditions:
- **Hutchinson-Gilford Progeria Syndrome** (HGPS), to reduce risk of mortality.
- **Progeroid laminopathies** that are processing-deficient, with either:
  - Heterozygous *LMNA* mutation with progerin-like protein accumulation; or
  - Homozygous or compound heterozygous *ZMPSTE24* mutations.[1]

Disease Overview

Hutchinson-Gilford Progeria Syndrome (HGPS)

HGPS is an ultra-rare, fatal, autosomal dominant genetic disorder with an estimated incidence of 1:4,000,000 live births and prevalence of 1:20,000,000 living individuals.[2] As of September 30, 2020, there were 18 patients identified with HGPS in the US.[3] HGPS results from a heterozygous mutation in *LMNA*, the gene encoding lamin A, a nuclear membrane protein.[4] "Classic" HGPS is caused by a single point mutation in *LMNA* involving c.1824C>T (G608G

mutation) and accounts for 90% of HGPS cases.[4,5] Other *LMNA* mutations have also been identified in either the exon 11 splice junction or intron 11; these increase activation of the cryptic splice site, thus producing progerin. These are referred to as "non-classic" HGPS and comprise the remaining 10% of HGPS cases (refer to Appendix). The mutated prelamin A is referred to as progerin. Accumulation of progerin causes stiffening of the nuclear membrane and disorganized nuclear pores and chromatin, leading to hallmark symptoms including rapidly progressive atherosclerosis. Severe, rapidly progressing atherosclerosis results in an average mortality at 14.6 years of age due to myocardial infarction or stroke.[4] It is estimated that 50% of affected children have had a radiographically detectable stroke by 8 years of age.

Progeroid Laminopathies

To date, over 400 mutations in the LMNA gene have been identified, giving rise to different laminopathies which encompass a range of phenotypes including muscular dystrophy, peripheral neuropathy, lipodystrophy, and premature aging diseases.[4] Some of these may have phenotypic overlap with HGPS ("progeroid" laminopathies).[5,6] In addition, pathogenic variants in *ZMPSTE24* can result in excess prelamin A proteins and a related phenotype. As of September 30, 2020, there were 13 patients identified with progeroid laminopathies in the US.[3] Of note; clinical data are not available regarding effect of Zokinvy in patients with progeroid laminopathies; the pivotal study only included patients with HGPS.

Guidelines

Formal guidelines for progeria are not in place. The Progeria Research Foundation provides a Progeria Handbook (updated March 2019) with information about the disease for patients and families, as well as for healthcare providers.[6] Clinical data with Zokinvy are acknowledged in the handbook as having positive results with regard to cardiovascular, bone, and survival outcomes. Diagnosis is made on the basis of clinical examination and genetic testing. It is noted that other progeroid laminopathies are closely related genetic diseases about which less is known. These conditions may be more or less severe than HGPS. Applying knowledge from classic progeria (i.e., HGPS) to other progeroid syndromes may be helpful, but good judgment must be applied since patients with other progeroid syndromes will have different needs.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zokinvy. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zokinvy as well as the monitoring required for adverse events and long-term efficacy, approval requires Zokinvy to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zokinvy is recommended in those who meet the following criteria:

FDA-Approved Indications

272. Hutchinson-Gilford Progeria Syndrome. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):

- **A)** Patient is ≥ 12 months of age; AND
- **B)** Patient has a body surface area of ≥ 0.39 m^2; AND
- **C)** Genetic testing demonstrates a confirmed pathogenic mutation in the *LMNA* gene consistent with Hutchinson-Gilford Progeria Syndrome; AND
  Note: Refer to Appendix for listing of genetic mutations associated with Hutchinson-Gilford Progeria Syndrome.
- **D)** The medication is prescribed by or in consultation with a geneticist or pediatric cardiologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zokinvy is not recommended in the following situations:

278. Progeroid Laminopathies. The efficacy of Zokinvy has not been established for patients with genetic disorders other than Hutchinson-Gilford Progeria Syndrome.[2] Although FDA labeling includes processing-deficient progeroid laminopathies, there are no clinical data demonstrating a treatment effect of Zokinvy in this population. Zokinvy is not indicated for use in processing-proficient progeroid laminopathies; based on its mechanism of action, Zokinvy would not be expected to be effective in this population.[1]

279. Other Progeroid Syndromes. Zokinvy is not indicated for use in other progeroid syndromes.[1] Based on its mechanism of action, Zokinvy would not be expected to be effective in this population.

280. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/20/2021

APPENDIX

Genetic mutations consistent with a diagnosis of Hutchinson-Gilford Progeria Syndrome are outlined below.[2,3] Of note, all of the following mutations are heterozygous; only one affected gene copy is required for confirmation of the diagnosis.

Appendix Table 1. Genetic Mutations Associated with Hutchinson-Gilford Progeria Syndrome.

Location on *LMNA* Gene	Mutation
Classic Hutchinson-Gilford Progeria Syndrome	
Exon 11	c.1824C>T; p.G608G
Non-Classic Hutchinson-Gilford Progeria Syndrome	
Exon 11	c.1821G>A; p.V607V
Exon 11	c.1822G>A; p.G608S
Exon 11	c.1868C>G; p.T623S
Intron 11	c.1968+1G>A
Intron 11	c.1968+1G>C
Intron 11	c.1968+2T>A
Intron 11	c.1968+2T>C

Intron 11	c.1968+5G>C