WELLFLEET

Prior Authorization Guidelines

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Revised: 1/1/2021

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

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]

- **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.
- **Collagen diseases**, during an exacerbation or as a maintenance therapy in selected cases of systemic lupus erythematosus (SLE) and systemic dermatomyositis (polymyositis).
- **Dermatologic diseases**, such as severe erythema multiforme and Stevens-Johnson syndrome.
- **Allergic states**, such as serum sickness.
- **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.
- **Respiratory diseases** such as symptomatic sarcoidosis.
- **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.

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.
- **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]
- **Kidney Disease Improving Global Outcomes (KDIGO)** published clinical practice guidelines for glomerulonephritis (2012).[6] Due to limited data, recommendations cannot be made regarding ACTH.

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) The child is less than 2 years of age; AND
   B) Acthar is prescribed by or in consultation with a neurologist.

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 given 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.

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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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PRIOR AUTHORIZATION POLICY

POLICY: Allergen Immunotherapy

- 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)

APPROVAL DATE: 07/10/2019

OVERVIEW

Grastek and Oralair are grass pollen allergen extract sublingual (SL) tablets indicated as immunotherapy for the treatment of patients 5 through 65 years of age with grass pollen-induced allergic rhinitis with or without conjunctivitis (AR/C).[1-2] Grastek, a Timothy grass pollen allergen extract, is indicated in patients with AR/C 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.[1] Oralair, a five-grass mixed pollens allergen extract, is indicated in patients with AR/C confirmed by a positive skin test or *in vitro* test for pollen-specific IgE antibodies for any of the five grasses contained in the product.[2] Grastek and Oralair are not indicated for the immediate relief of allergy symptoms. In clinical trials, therapy with the grass pollen SL 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 AR/C 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. The 2015 American Academy of Otolaryngology (AAO) and the 2011 Joint Taskforce of The American Academy of Allergy, Asthma, and Immunology (AAAAI), the American College of Allergy, Asthma, and Immunology (ACAAI), and the Joint Council of Allergy, Asthma and Immunology (JCAAI) Practice Parameter for Allergen Immunotherapy states 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.[3,4] The European Academy of Allergy and Clinical Immunology (EAACI) guidelines on allergen immunotherapy for allergic rhinitis (2018) make similar recommendations and also specifically recommend grass pollen SLIT tablets for both short-term and long-term benefit in grass pollen-induced AR/C.[21] In 2017, a Joint Practice Parameter specifically addressing SL immunotherapy was published.[5] FDA-approved SL immunotherapy agents, including Grastek and Oralair, are recommended to be used only for the treatment of AR/C and not for other off-label conditions.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of the sublingual grass pollen immunoallergen extracts. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Grastek and Oralair are recommended in those who meet the following criteria:

FDA-Approved Indications

2. **Grass Pollen-Induced Allergic Rhinitis (AR).** Approve for 1 year if the patient meets ALL of the following criteria (A, B and C):
   D) The patient is ≥ 5 years of age;[1,6-8] AND
   E) The timing of prescribing meets ONE of the following criteria (i or ii):[1,2]
      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
   F) The diagnosis of grass pollen-induced AR is confirmed by meeting ONE of the following conditions (i or ii):[6-20]
      i. The 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. The 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
Grastek and Oralair 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.)

8. **Concurrent use of Grastek or Oralair with subcutaneous (SC) allergen immunotherapy (e.g., allergy shots) or sublingual (SL) 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 SC or SL allergen immunotherapy. A Joint Practice Parameter specifically addressing SL immunotherapy (2017) highlights that no studies have evaluated the efficacy of multiple SLIT tablets administered together.[5] There is a need for further investigation to determine efficacy and optimal formulations for multi-allergen SL 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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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

3. **House Dust Mite-Induced Allergic Rhinitis.** Approve for 1 year if the patient meets ALL of the following criteria (A and B):
   G) Patient is ≥ 18 years of age; AND
   H) 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:

10. **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.

11. 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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PRIOR AUTHORIZATION POLICY

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

DATE REVIEWED: 02/12/2020

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

One Phase III, randomized, double-blind, placebo-controlled pivotal study, PALISADE (published) [n = 551 {n = 496 patients 4 to 17 years of age in the intent-to-treat (ITT) analysis}], established the efficacy of Palforzia in patients with peanut allergy.[2] To be eligible for PALISADE, 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. In the cohort of patients 4 to 17 years of age, the median baseline wheal diameter on SPT was 11 mm and the median baseline level of psIgE was 71 kUA/L. 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 then randomized (3:1) to receive either Palforzia or matching placebo administered once daily (QD).[2] Patients underwent an Initial Dose Escalation and Up-Dosing over 20 to 40 weeks until a dose of 300 mg was reached. Maintenance therapy of Palforzia 300 mg QD (or placebo equivalent) was then administered for 24 weeks. At the end of the maintenance period, patients underwent an exit DBPCFC to assess their tolerance to peanut protein. The primary efficacy endpoint was the proportion of patients who were able to tolerate the single dose of 600 mg of peanut protein (equivalent to approximately two whole peanut kernels) or more during the exit DBPCFC, with no dose-limiting symptoms. In patients 4 to 17 years of age, 67.2% of patients receiving Palforzia (n = 250/372) met the primary endpoint compared with 4.0% (n = 5/124) with placebo (treatment difference: 63.2% [confidence interval {CI}: 53.0%, 73.3%]; P < 0.001).

Guidelines

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] state that medical history and a physical examination should guide the diagnosis.[4] Even in patients

in whom food-allergy is suspected, it is stated that parent and patient reports of food allergy must be confirmed, as multiple studies have shown that 50% to 90% of patient-reported food allergies are not IgE-mediated food allergies. Performing a SPT is recommended to assist in the identification of foods that may be causing IgE-mediated food-induced allergic reactions, but the SPT alone cannot be considered diagnostic for food allergy. Allergen-specific IgE testing is also recommended to identify foods that potentially provoke IgE-mediated food-induced allergic reactions. However, again, these tests alone are not considered to be diagnostic of 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); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology (JCAAI) [2014][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.

Automation: None.

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

FDA-Approved Indications

4. **Peanut Allergy.** Approve Palforzia for 1 year if the patient meets ALL of the following criteria (A, B, C, D, E, and F):
   - **I)** The 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
   - **J)** The medication is prescribed by or in consultation with an allergist or immunologist; AND
   - **K)** 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.** The 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.
   - **L)** The patient has a positive skin prick test (SPT) response to peanut with a wheal diameter ≥ 3 mm larger than the negative control; AND
   - **M)** The 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
   - **N)** Per the prescriber, Palforzia will be used in conjunction with a peanut-avoidant diet.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Palforzia 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.

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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

5. **Short Ragweed Pollen-Induced Allergic Rhinitis.** Approve for 1 year if the patient meets ALL of the following criteria (A, B and C):
   - **O)** Patient is ≥ 18 years of age;[1] AND
   - **P)** Ragwitek therapy is initiated 12 weeks prior to the expected onset of the short ragweed pollen season; AND
   - **Q)** 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:

13. **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.

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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PRIOR AUTHORIZATION POLICY

POLICY: Alpha$_1$-Proteinase Inhibitor Products

- 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)

APPROVAL DATE: 10/09/2019

OVERVIEW

Alpha$_1$-proteinase inhibitor (also known as alpha$_1$-antitrypsin [AAT]), is indicated for use as a chronic replacement or augmentation therapy for individuals with a congenital deficiency of AAT with clinically demonstrable emphysema.[1-5] In the scientific literature, the disorder is referred to as AAT deficiency whereas the deficiency or replacement protein is referred to as alpha$_1$-proteinase inhibitor. 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.

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 American Thoracic Society (ATS) and ERS standards for the diagnosis and management of individuals with AAT deficiency (updated in 2003), 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 for those who meet the following criteria.

FDA-Approved Indications

1. **Alpha$_1$-Antitrypsin Deficiency with Emphysema (or COPD).** Approve for 1 year in patients meeting the following criteria (A and B):
   - **A)** The patient has a baseline (pretreatment) AAT serum concentration of < 80 mg/dL or 11 μM (11 μmol/L); AND

B) According to the prescriber, the patient is a current non-smoker.

Other Uses with Supportive Evidence

2. AAT Deficiency-Associated Panniculitis. Approve for 1 year.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Alpha$_1$-proteinase inhibitor 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. **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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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

6. **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
1. Firdapse® tablets [prescribing information]. Coral Gables, FL: Catalyst Pharmaceuticals, Inc.; November 2018.
2. Ruzurgi® tablets [prescribing information]. Princeton, NJ: Jacobus Pharmaceutical Company, Inc.; May 2019.
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PRIOR AUTHORIZATION POLICY

POLICY: Amyloidosis – Onpattro (patisiran intravenous injection – Alnylam)

APPROVAL DATE: 10/16/2019

OVERVIEW
Onpattro is a lipid nanoparticle formulated RNA interference (RNAi) therapeutic indicated for treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) in adults.[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 causes degradation of mutant and wild-type TTR mRNA through RNA interference, which results in a reduction of serum TTR protein and TTR protein deposits in tissues.[1]

Guidelines
There is a European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy (2016).[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 stablizers (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]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Onpattro. Because 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, initial approval requires Onpattro 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 Onpattro is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Polyneuropathy of Hereditary Amyloid Transthyretin–Mediated Amyloidosis (hATTR).** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** The patient has a transthyretin (TTR) mutation as confirmed by genetic testing; AND
   - **B)** The patient has symptomatic peripheral neuropathy.
     Note: Examples of symptomatic peripheral neuropathy include reduced motor strength/ coordination, impaired sensation (e.g., pain, temperature, vibration, touch); AND
   - **C)** The 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.
     Note: Examples of gabapentin-type products include gabapentin (Neurontin) and Lyrica pregabalin (Lyrica). Examples of tricyclic antidepressants include amitriptyline and nortriptyline; AND
   - **D)** The patient is 18 years of age or older; AND
   - **E)** Onpattro 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

Onpattro 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.)

15. **Concomitant Use With Tegsedi (inotersen subcutaneous injection) or a Tafamidis Product.** Note: examples of tafamadis products are Vynaqel 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).

16. 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 injection [prescribing information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; September 2019.
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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.
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PRIOR AUTHORIZATION POLICY

POLICY: Amyloidosis – Tafamidis Products

- Vyndaqel (tafamidis meglumine capsules – Pfizer)

- Vyndamax (tafamidis capsules – Pfizer)

APPROVAL DATE: 10/23/2019

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

2. **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)** The 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.** The patient had genetic testing which, according to the prescriber, identified a TTR mutation. Note: Examples of TTR mutations include Val122Ile mutation and Thr60Ala mutation. If the patient has wild-type amyloidosis, this is **not** a TTR mutation; AND
   - **C)** Diagnostic cardiac imaging has demonstrated cardiac involvement. 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; AND
   - **D)** The patient has heart failure, but does **not** have New York Heart Association class IV disease; AND
   - **E)** The agent is prescribed by or in consultation with a cardiologist or a physician who specializes in the treatment of amyloidosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Tafamidis products (Vyndaqel and Vyndamax) 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. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

17. **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).

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

19. **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.

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. 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.
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PRIOR AUTHORIZATION POLICY

POLICY: Amyloidosis – Tegsedi™ (inotersen injection for subcutaneous use – Ionis/Akcea Therapeutics)

APPROVAL DATE: 10/16/2019

OVERVIEW

Tegsedi is 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 stablizers (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]

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. Platelets should be monitored prior to starting therapy and during treatment as directed in the prescribing information. Do not administer to any patient with signs or symptoms of thrombocytopenia unless results are interpretable and acceptable to a medical professional. 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 a the Tegsedi REMS (Risk Evaluation and Mitigation Strategy.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Tegsedi. 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, initial approval requires Tegsedi 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 Tegsedi is recommended in those who meet the following criteria:

FDA-Approved Indications

3. **Polyneuropathy of Hereditary Transthyretin–Mediated Amyloidosis (hATTR).** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** The patient has a transthyretin (TTR) mutation as confirmed by genetic testing; AND
   - **B)** The patient has symptomatic peripheral neuropathy.
     Note: Examples of symptomatic peripheral neuropathy include reduced motor strength/ coordination, impaired sensation (e.g., pain, temperature, vibration, touch); AND
   - **C)** The 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.
     Note: Examples of gabapentin-type products include gabapentin (Neurontin) and pregabalin (Lyrica). Examples of tricyclic antidepressants include amitriptyline and nortriptyline; AND
   - **D)** The patient is 18 years of age or older; AND
   - **E)** Tegsedi 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

Tegsedi 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.)

21. **Concomitant Use With Onpattro (patisiran lipid complex intravenous infusion) or a Tafamidis Product.** Note: examples of tafamadis products are Vynaqel 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).

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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10. Onpattro injection [prescribing information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.; August 2018.
11. Ando Y, Coelho T, Berk JL. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare Dis.* 2013;8:31.
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PRIOR AUTHORIZATION POLICY

POLICY: Antibiotics – Linezolid (Zyvox), Sivextro PA Policy
- Linezolid tablets, oral suspension (Zyvox® – Pfizer, generics)
- Sivextro™ (tedizolid phosphate tablets – Cubist Pharmaceuticals)

REVIEW DATE: 10/09/2019

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 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]
- Vancomycin-resistant *Enterococcus faecium* (VRE) infections, including cases with concurrent bacteremia;
- Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible [MSSA] and methicillin-resistant strains [MRSA]), or *Streptococcus pneumoniae*;
- 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;
- Uncomplicated skin and skin structure infections (SSTIs) caused by *S. aureus* (MSSA only) or *S. pyogenes*; and
- Community-acquired pneumonia (CAP**)** caused by *S. pneumoniae*, including cases with concurrent bacteremia, or *S. aureus* (MSSA only).

Sivextro is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults 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

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

Diabetic Foot Infections
A clinical practice guideline for the diagnosis and treatment of diabetic foot infections (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).

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.

Pneumonia
Guidelines from the American Thoracic Society (ATS) and IDSA (2016) recommend that MRSA hospital-aquired 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 prooducts. Guidelines from the IDSA/ATS (2007) for community-acquired pneumonia (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]

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]

POLICY STATEMENT
Prior authorization is recommended for prescription benefit coverage of Zyvox 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) The patient is transitioning from intravenous (IV) linezolid or IV vancomycin to oral linezolid therapy; OR
   b) The 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 Prescribing Physician 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 prescribing physician or representative of the physician 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 Prescribing Physician 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 prescribing physician or representative of the physician 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

Linezolid and Sivextro 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.

23. 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.

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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

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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.

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

PRIOR AUTHORIZATION POLICY

POLICY: Antibiotics (Inhaled) – Arikayce Prior Authorization Policy
- Arikayce® (amikacin liposome inhalation suspension for oral inhalation – Insmed)

REVIEW DATE: 10/23/2019; selected revision 6/24/2020

OVERVIEW
Arikayce is indicated in adults for the treatment of *Mycobacterium avium* complex (MAC) lung disease, in those 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 person 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
According to the American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA) statement on the Diagnosis, Treatment and Prevention of Nontuberculous Mycobacterial Disease (2007 version), the role of inhaled antibiotics such as amikacin has not been established.[6] The guidelines do not mention liposomal amikacin.

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 (1.56% and 2.87%, respectively, P = 0.48). The mean difference was -1.31% (95% confidence interval [CI]: -4.95, 2.34) 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 (63.5% vs. 51.4%, respectively, P = 0.02); however, fewer patients required all-cause hospitalization (16.2% vs. 19.9%). 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 (1.2 and 1.7) and at Day 140 (1.5 and 1.6).

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

4. ***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.
Note: A multidrug regimen typically include a macrolide (azithromycin or clarithromycin), ethambutol, and a rifamycin (rifampin or rifabutin); AND
C) Arikayce will be used in conjunction to a background multidrug regimen.
Note: A multidrug regimen typically include a macrolide (azithromycin or clarithromycin), ethambutol, and a rifamycin (rifampin or rifabutin); AND
D) Arikayce 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

5. 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) Arikayce 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:

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

11. Arikayce [prescribing information]. South San Francisco, CA and Whitby, Ontario: Rigel Pharmaceuticals and Pantheon Whitby; September 2018.
12. Adjemian J, Daniel-Wayman S, Ricotta E, Prevots DR. Epidemiology of Nontuberculous Mycobacteriosis. *Semin Respir Crit Care Med*. 2018;39:325-335.
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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

6. **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

7. **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.

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

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

21. Cayston inhalation solution [prescribing information]. Foster City, CA: Gilead Sciences; November 2019.

22. Flume PK, O'Sullivan BP, Robinson KA, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2007;176:957-969.
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26. 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.
27. Mogayzel PJ, Naureckas ET, Robinson KA, et al; and the Cystic Fibrosis Foundation Pulmonary Clinical Practice Guidelines Committee. Pharmacologic approaches to prevention and eradication of initial *Pseudomonas aeruginosa* infection. *Ann Am Thorac Soc*. 2014;11(10):1640-1650.

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

8. 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

9. 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.

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
28. TOBI® Podhaler inhalation powder [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; October 2015.
29. Flume PK, O'Sullivan BP, Robinson KA, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2007;176:957-969.
30. Le J, Ashley ED, Neuhauser MM, et al and the Society of Infectious Diseases Pharmacists Aerosolized Antimicrobials Task Force. Consensus summary of aerosolized antimicrobial agents: application of guideline criteria. Insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy*. 2010;30(6):562-584.
31. Geller DE. Aerosol antibiotics in cystic fibrosis. *Respir Care*. 2009;54(5):658-669.
32. 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.
33. Mogayzel PJ, Naureckas ET, Robinson KA, et al; and the Cystic Fibrosis Foundation Pulmonary Clinical Practice Guidelines Committee. Pharmacologic approaches to prevention and eradication of initial *Pseudomonas aeruginosa* infection. *Ann Am Thorac Soc*. 2014;11(10):1640-1650.
34. McShane PJ, Naureckas ET, Tino G, Strek ME. Non-cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med*. 2013;188:647-656.
35. Polverino E, Goeminne PC, McDonnell, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J*. 2017;50:1700629.

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

10. 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

11. 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.

12. 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.

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

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

36. TOBI® inhalation solution [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; October 2018.
37. Kitabis™ inhalation solution [prescribing information]. Woodstock, IL: Catalent Pharma Solutions; December 2019.
38. Bethkis® inhalation solution [prescribing information]. Woodstock, IL: Chiesi USA/Catalent Pharma Solutions; December 2019.
39. Flume PK, O'Sullivan BP, Robinson KA, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2007;176:957-969.
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42. 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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44. Barker AF, Couch L, Fiel SB, et al. Tobramycin solution for inhalation reduces sputum *Pseudomonas aeruginosa* density in bronchiectasis. *Am J Respir Crit Care Med*. 2000;162:481-485.
45. Orriols R, Hernando R, Ferrer A, et al. Eradication therapy against *Pseudomonas aeruginosa* in non-cystic fibrosis bronchiectasis. *Respiration*. 2015;90:299-305.
46. Drobnic ME, Sune P, Montoro JB, et al. Inhaled tobramycin in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection with *Pseudomonas aeruginosa*. *Ann Pharmacother*. 2005;39:39-44.
47. Scheinberg P, Shore E. A pilot study of the safety and efficacy of tobramycin solution for inhalation in patients with severe bronchiectasis. *Chest*. 2005;127:1420-1426.
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49. Polverino E, Goeminne PC, McDonnell, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J*. 2017;50:1700629.

OTHER REFERENCES UTILIZED

- Orriols R, Roig J, Ferrer J, et al. Inhaled antibiotic therapy in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection by *Pseudomonas aeruginosa*. *Respir Med*. 1999;93:476-480.
- Bilton D, Henig N, Morrissey B, Gotfried M. Addition of inhaled tobramycin to ciprofloxacin for acute exacerbations of *Pseudomonas aeruginosa* infection in adult bronchiectasis. *Chest*. 2006;130:1503-1510.

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
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

Generic	Brand	Manufacturer
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
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:

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

14. 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.

PRIOR AUTHORIZATION POLICY

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

DATE REVIEWED: 11/13/2019

OVERVIEW
Eliquis is a Factor Xa inhibitor anticoagulant indicated for the following:

- To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation;
- For the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery; and
- For the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy.[1]

Of note, the recommended duration of Eliquis treatment is 35 days for hip surgery and 12 days for knee surgery. Like other oral anticoagulants, Eliquis has a Boxed Warning that premature discontinuation increases the risk of thrombotic events and that spinal/epidural hematomas may occur in patients treated with Eliquis who are receiving neuraxial anesthesia or undergoing spinal puncture.

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]

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.

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 high-risk patients).** Approve for 6 months if the patient meets ONE of the following criteria (A or B):
   - **A)** The patient meets one of the following for the condition (i or ii):
     - **i.** The patient has tried warfarin, fondaparinux injection, or a low molecular weight heparin product (e.g., enoxaparin injection, Fragmin® [dalteparin injection]); OR
     - **ii.** The patient has tried Xarelto® (rivaroxaban tablets), Pradaxa® (dabigatran capsules), or Savaysa® (edoxaban tablets); OR
   - **B)** The patient has been started on Eliquis for the treatment of an acute thromboembolic condition.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Eliquis 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. **Use After an Acute Coronary Syndrome to Reduce the Potential for Thrombotic Events.** (Note: Examples of acute coronary syndromes include unstable angina, non-ST elevation myocardial infarction [MI], and ST elevation MI. Examples of thrombotic events include cardiovascular death, MI, or stroke.)
   The APPRAISE-2 trial was terminated after it was found that the addition of Eliquis to antiplatelet therapy in high-risk patients after an ACS event increased the number of major bleeding events without a significant reduction in recurrent ischemic events.[7] Note: If the patient has a history of an ACS (condition not recommended for approval), but is requesting Eliquis for a non-ACS condition, approval can be considered if criteria are met.

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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PRIOR AUTHORIZATION POLICY WITH PREFERRED STEP THERAPY

POLICY: Anticoagulants – Pradaxa® (dabigatran capsules – Boehringer Ingelheim)

DATE REVIEWED: 11/13/2019

OVERVIEW

Pradaxa is a direct thrombin inhibitor. It has the following indications:

- To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation;

- For the 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;
- To reduce the risk of recurrence of DVT and PE in patients who have been previously treated; and
- For the prophylaxis of DVT and PE in patients who have undergone hip replacement surgery.[1]

After hip replacement surgery, up to 35 days of DVT/PE prophylaxis is recommended.[1] Like other oral anticoagulants, Pradaxa has a Boxed Warning that premature discontinuation increases the risk of thrombotic events and that spinal/epidural hematomas may occur in patients treated with Eliquis who are receiving neuraxial anesthesia or undergoing spinal puncture.

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]

Other Uses with Supportive Evidence

Pradaxa has data supporting its use in prophylaxis after knee replacement surgery.[7-9] 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 PA Policy also contains a Preferred Step Therapy component. When clinically appropriate, patients are directed to try one Preferred Step 1 agent (Eliquis® [apixaban tablets] or Xarelto® [rivaroxaban tablets]) prior to Pradaxa (Step 2). All approvals are provided for the duration noted below. If the patient meets the criteria for the diagnosis stated but has not tried the Preferred Step 1 agent, approvals are provided for the Step 1 agent.

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) The patient has tried Eliquis or Xarelto; OR
   B) The 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) The patient has tried Eliquis or Xarelto; OR
    B) The 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) The patient has tried Eliquis or Xarelto; OR
    B) The 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) The patient meets one of the following for the condition (i or ii):
       i. The patient has tried warfarin, fondaparinux, or a low molecular weight heparin (LMWH) product (e.g., enoxaparin, Fragmin® [dalteparin injection]); OR
       ii. The patient has tried Eliquis or Xarelto; OR
    D) The patient has been started on Pradaxa for the treatment of an acute thromboembolic condition.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Pradaxa 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.)

26. **Mechanical Prosthetic Heart Valves (To Prevent Thromboembolic Complications).** Pradaxa is contraindicated in patients with mechanical prosthetic heart valves.[1] The safety and efficacy of Pradaxa in patients with a bileaflet mechanical prosthetic heart valve was evaluated in the RE-ALIGN (Randomized, Phase II study to Evaluate the sAfety and pharmacokinetics of oraL dabIGatran etexilate in patients after heart valve replacemeNt) study.[1,10,11] RE-ALIGN was terminated early because there were significantly more thromboembolic events (valve thrombosis, stroke, transient ischemic attack, and myocardial infarction) and an excess of major bleeding in patients randomized to Pradaxa compared to those randomized to warfarin. The FDA recommends that health care professionals should promptly transition any patient with a mechanical heart valve who is receiving Pradaxa to take another medication.[10]

27. Use After an Acute Coronary Syndrome to Reduce the Potential for Thrombotic Events. (Note: Examples of acute coronary syndromes include unstable angina, non-ST elevation myocardial infarction [MI], or ST elevation MI. Examples of thrombotic events include cardiovascular death, MI, or stroke.)
In a Phase II dose-ranging study (n = 1,861), Pradaxa added on to dual antiplatelet therapy significantly increased risk of bleeding in a dose-dependent manner vs. dual antiplatelet therapy alone.[12] The study was not designed to detect an efficacy difference in ischemic event rates; 14 patients died, had an MI, or had a stroke in the placebo group vs. 12 patients in the Pradaxa 150 mg group.

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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PRIOR AUTHORIZATION POLICY WITH PREFERRED STEP THERAPY

POLICY: Anticoagulants – Savaysa® (edoxaban tablets – Daiichi Sankyo)

DATE REVIEWED: 11/13/2019

OVERVIEW

Savaysa, a Factor Xa inhibitor, is indicated for the following:

- To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; and
- For the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5 to 10 days of initial therapy with a parenteral anticoagulant.[1]

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. Other Boxed Warnings are similar to the other direct oral anticoagulants (DOACs): premature discontinuation increases the risk of ischemic events, and spinal/epidural hematoma may occur in patients treated with Savaysa who are receiving neuraxial anesthesia or undergoing spinal puncture. The safety and efficacy of Savaysa has not been studied in patients with mechanical heart values or moderate to severe mitral stenosis. Use of Savaysa is not recommended in these patients.

Guidelines

Guidelines are available which support the use of 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]

Regarding DVT/PE, Savaysa has been used for cancer-associated venous thromboembolism (VTE) and is listed as an option for combination therapy (after at least 5 days of parenteral anticoagulation) in National Comprehensive Cancer Network guidelines (version 1.2019 – February 28, 2019) [category 1 recommendation].[4] Other DOACs are listed as alternatives, but are not category 1 recommendations. Efficacy of Savaysa in cancer-associated VTE was established in the Hokusai VTE Cancer trial (n = 1,046), in which edoxaban demonstrated non-inferiority vs. subcutaneous Fragmin® (dalteparin injection) in the composite outcome of recurrent VTE or major bleeding.[7]

Other Uses with Supportive Evidence

Savaysa has data for prophylaxis of VTE after hip replacement surgery.[8] 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 Preferred Step Therapy component. When clinically appropriate, patients are directed to try one Step 1 agent (Eliquis® [apixaban tablets] or Xarelto® [rivaroxaban tablets]) prior to Savaysa (Step 2). All

approvals are provided for the duration noted below. If the patient meets the criteria for the diagnosis stated but has not tried the Step 1 agent, approvals are provided for the Step 1 agent.

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) The patient has an estimated creatinine clearance (CrCl) ≤ 95 mL/min; AND
    D) The 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, B, or C):
    A) The patient has tried Eliquis or Xarelto; OR
    B) The medication is being used for deep vein thrombosis or pulmonary embolism associated with cancer; OR
    C) The 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) The patient has tried Eliquis or Xarelto; OR
    D) The 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) The patient meets one of the following for the condition (i or ii):
        i. The patient has tried warfarin, fondaparinux, or a low molecular weight heparin product (e.g., enoxaparin, Fragmin® [dalteparin injection]); OR
        ii. The patient has tried Xarelto or Eliquis; OR
    F) The patient has been started on Savaysa for the treatment of an acute thromboembolic condition.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Savaysa 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.)

29. **Use After an Acute Coronary Syndrome to Reduce the Potential for Thrombotic Events.** No data support the role of Savaysa at this time for use in acute coronary syndrome (ACS) without other reasons for anticoagulation (e.g., atrial fibrillation). Other alternative, proven, effective, established therapies that are detailed in nationally-recognized guidelines are available for those who have experienced an ACS. Note: If the patient has a history of an ACS (condition not recommended for approval) but is requesting Savaysa for a non-ACS condition, approval can be considered if criteria are met.

30. 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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PRIOR AUTHORIZATION POLICY

POLICY: Anticoagulants – Xarelto® (rivaroxaban tablets – Janssen)

DATE REVIEWED: 11/13/2019

OVERVIEW

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

- To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation;
- For the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE);
- For the 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;
- For the prophylaxis of DVT, which may lead to PE, in patients undergoing knee or hip replacement surgery;

- For the prophylaxis of venous thromboembolism in acutely ill medical patients at risk for thromboembolic complications not at high risk of bleeding; and
- In combination with aspirin, to reduce the risk of major adverse cardiovascular (CV) events (CV death, myocardial infarction, and stroke) in patients with chronic coronary artery disease or peripheral arterial disease.

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]

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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indications

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

2. **Deep Vein Thrombosis in Patients 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, Patients with Coronary Artery Disease or Peripheral Artery Disease.** Approve for 1 year if the patient will also concomitantly be taking aspirin at least 75 mg daily.

6. **Venous Thromboembolism in Acutely Ill Medical Patients, Prophylaxis.** Approve for 60 days.

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 high-risk patients).** Approve for 6 months if the patient meets ONE of the following criteria (A or B):
   - **A)** The patient meets one of the following for the condition (i or ii):
     - **i.** The patient has tried warfarin, fondaparinux or a low molecular weight heparin (LMWH) product (e.g., enoxaparin, Fragmin® [dalteparin injection]); OR
     - **ii.** The patient has tried Eliquis® (apixaban tablets), Pradaxa® (dabigatran capsules), or Savaysa® (edoxaban tablets); OR
   - **B)** The patient has been started on Xarelto for the treatment of an acute thromboembolic condition.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Xarelto 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.)

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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PRIOR AUTHORIZATION POLICY

POLICY: Antiepileptics – Banzel® (rufinamide tablets and oral suspension – Eisai)

APPROVAL DATE: 09/18/2019

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] Banzel is a triazole derivative structurally unrelated to currently marketed antiepileptic drugs (AEDs). 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.

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.

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 (or 26 out of 100,000).[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 (eg. 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 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. The patient is ≥ 1 year of age; AND
     ii. The patient has tried and/or is concomitantly receiving at least two other antiepileptic drugs; AND
     iii. Banzel is prescribed by, or in consultation with, a neurologist.

     Note: Examples of antiepileptic drugs include valproic acid, gabapentin, phenytoin, carbamazepine, oxcarbazepine, lacosamide, levetiracetam, zonisamide, Fycompa, vigabatrin, lamotrigine, topiramate, clobazam, Diacomit, Epidiolex, and felbamate.
   - **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 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. The patient is ≥ 1 years of age; AND
     ii. The patient has tried and/or is concomitantly receiving at least two other antiepileptic drugs; AND
     iii. Banzel is prescribed by, or in consultation with, a neurologist.

     Note: Examples of antiepileptic drugs include valproic acid, gabapentin, phenytoin, carbamazepine, oxcarbazepine, lacosamide, levetiracetam, zonisamide, Fycompa, vigabatrin, lamotrigine, topiramate, clobazam, Diacomit, Epidiolex, and felbamate.
   - **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

Banzel 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.

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Other References Utilized:

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PRIOR AUTHORIZATION POLICY

POLICY: Antiepileptics – Clobazam Products

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

DATE REVIEWED: 11/20/2019

OVERVIEW

Clobazam is a benzodiazepine. 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. 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]

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 (or 26 out of 100,000).[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 AEDs, dietary therapy (typically the ketogenic diet), and device/surgery (eg. 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 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.[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 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, stiripentol (not available in the US, but can be obtained from foreign countries) and topiramate are second-line treatment. 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. Sodium channel blockers (e.g., carbamazepine, oxcarbazepine, lamotrigine, and phenytoin can worsen seizures in Dravet syndrome. Additionally, Sabril® (vigabatrin tablet, oral packet) and tiagabine may increase the frequency of myoclonic seizures and should be avoided.

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.[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. The patient is ≥ 2 years of age; AND
     ii. The 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 (e.g., reduced seizure severity, frequency, and/or duration from baseline [prior to initiation of clobazam]) as determined by the prescriber.

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 iii)
     i. The 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 (e.g., reduced seizure severity, frequency, and/or duration from baseline [prior to initiation of clobazam]) as determined by the prescriber.

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):
     iv. The patient is ≥ 2 years of age; AND
     v. The patient has tried and/or is concomitantly receiving at least two other antiepileptic drugs (e.g., valproic acid, lamotrigine, topiramate, clonazepam, levetiracetam, zonisamide, Banzel, felbamate); AND
     vi. 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 (e.g., reduced seizure severity, frequency, and/or duration from baseline [prior to initiation of clobazam]) as determined by the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Clobazam 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.)

32. 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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PRIOR AUTHORIZATION POLICY

POLICY: Antiepileptics – Diacomit® (stiripentol capsules and powder for oral suspension – Biocodex)

DATE REVIEWED: 01/29/2020; selected revision 05/20/2020

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. There are no clinical data to support the use of

Diacomit as monotherapy in Dravet syndrome. The mechanism by which Diacomit exerts its anticonvulsant effect is not known. Possible mechanisms of action include direct effects mediated through the gamma-aminobutyric acid $(GABA)_A$ receptor and indirect effects involving inhibition of cytochrome P450 (CYP) activity with resulting increase in blood levels of clobazam and its active metabolite.

Disease Overview

Dravet syndrome is a rare genetic epileptic encephalopathy (dysfunction of the brain) marked with frequent and/or prolonged seizures.[2,3] 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.[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.

Clinical Efficacy in Other Refratory 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, multicenter, 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

Valproic acid and clobazam are considered to be the first-line treatment for Dravet syndrome.[2,4,5] If seizure control is suboptimal, Diacomit and topiramate are second-line treatment. Ketogenic diet is moderately effective and can also be considered second-line. If control is still inadequate, other therapies to consider are clonazepam, levetiracetam, and zonisamide. Sodium channel blockers (e.g., carbamazepine, oxcarbazepine, lamotrigine, and phenytoin can worsen seizures in Dravet syndrome. Additionally, Sabril® (vigabatrin tablet, oral packet for suspension [generics]) and tiagabine may increase the frequency of myoclonic seizures and should be avoided.

Safety

The most common AEs in patients treated with Diacomit in the placebo-controlled studies were somnolence (67%), decreased appetite (45%), agitation (27%), ataxia (27%), weight decreased (27%), hypotonia (24%),

nausea (15%), tremor (15%), dysarthria (12%), and insomnia (12%). Hematologic testing should be obtained prior to starting treatment with Diacomit and every 6 months. During a clinical trial, a decrease in neutrophil count from normal at baseline to < 1,500 cells/mm^3 was observed in 13% of patients treated with Diacomit but not in patients treated with placebo. Also during this clinical trial, a decrease in platelet count from normal at baseline to < 150,000/μL during the trial was observed in 13% of these patients but not in patients on placebo.

Diacomit powder for suspension contains phenylalanine, a component of aspartame. Each 250 mg packet contains 1.4 mg phenylalanine; each 500 mg packet contains 2.8 mg phenylalanine. Consider the combined daily amount of phenylalanine from all sources, including Diacomit, in patients with phenylketonuria (PKU). Diacomit capsules do not contain phenylalanine.

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 long-term 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):
      iii. The patient is ≥ 2 years of age; AND
      iv. The patient meets ONE of the following criteria (a or b):
         a. The patient is taking concomitant clobazam; OR
         b. The patient is unable to take clobazam due to adverse events as determined by the prescriber; AND
      v. Diacomit 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)
      vii. The patient is ≥ 2 years of age; AND
      viii. The patient has tried at least two other antiepileptic drugs; AND

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

ix. Diacomit 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

Diacomit 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.)

33. 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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PRIOR AUTHORIZATION POLICY

POLICY: Antiepileptics – Epidiolex Prior Authorization Policy

- Epidiolex® (cannabidiol oral solution – GW Pharmaceuticals)

REVIEW DATE: 01/29/2020; selected revision 05/20/2020 and 08/12/2020

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 only two drugs approved for the treatment of seizures associated with Dravet syndrome: Epidiolex and Diacomit® (stiripentol capsules, powder for oral suspension).[1,11] Valproic acid (Depakote® tablet, generic; Depakote® ER tablet, generic; Depakote® Sprinkle capsule; Depakene® capsule, oral solution, generic) and clobazam (Onfi® tablets, oral suspension, generic; Sympazan™ oral film) are considered to be the first-line treatment for Dravet syndrome.[2,4] If seizure control is suboptimal, Diacomit and topiramate (Topamax® tablet, generic; Topamax® Sprinkle capsule, generic; Qudexy® XR capsule; Trokendi XR™ capsule) are second-line treatment. Ketogenic diet is moderately effective and can also be considered second-line. If control is still inadequate, other therapies to consider are clonazepam (Klonopin® tablet, generic; clonazepam orally disintegrating tablet), levetiracetam (Keppra® tablet, oral solution, generic; Keppra XR®, generic), and zonisamide (Zonegran® capsule, generic). Sodium channel blockers (e.g., carbamazepine [Tegretol® tablet, oral suspension, generic; Tegretol® XR tablet, generic; Carbatrol® capsule, generic; Equetro® capsule], oxcarbazepine [Trileptal® tablet, oral suspension, generic; Oxtellar XR® tablet], lamotrigine (Lamictal® tablet, generic; Lamictal® XR™ tablet, generic; Lamictal ODT®, generic), and phenytoin [Dilantin® capsule, oral suspension, generic; Infatabs® Dilantin® chewable tablet, generic] can worsen seizures in Dravet syndrome. Additionally, Sabril® (vigabatrin tablet, oral packet [available generically]) and tiagabine (Gabitril® tablet, generic) may increase the frequency of myoclonic seizures and should be avoided.

Lennox-Gastaut Syndrome

Currently, the FDA-approved drugs for this condition are felbamate tablet, oral suspension (Felbatol®, generic), 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 1 year in duration unless otherwise 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)
   vi. Patient is ≥ 1 years of age; AND
   vii. Patient has tried at least two other antiepileptic drugs OR one of Diacomit or clobazam; AND
   Note: Examples of other antiepileptic drugs include valproic acid, topiramate, clonazepam, levetiracetam, zonisamide, others.
   viii. Epidiolex 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 has tried at least two other antiepileptic drugs OR one of lamotrigine, topiramate, Banzel, felbamate, clobazam; AND
   Note: Examples of other antiepileptic drugs include valproic acid, levetiracetam, zonisamide, Fycompa, vigabatrin, others.
   iii. Epidiolex 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, others.
   iii. Epidiolex 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):
     - x. Patient is ≥ 1 years of age; AND
     - xi. 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.
     - xii. Epidiolex 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.

REFERENCES

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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

13. 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:

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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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

14. 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:

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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PRIOR AUTHORIZATION POLICY

POLICY: Antiepileptics – Valtoco® (diazepam nasal spray – Neurelis)

DATE REVIEWED: 02/05/2020

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] The exact mechanism of action is not fully understood, but it is thought to involve potentiation of gamma-aminobutyric acid (GABA)ergic neurotransmission resulting from binding at the benzodiazepine site of the $GABA_A$ receptor. The maximum plasma diazepam concentrations after nasal administration of Valtoco is reached in approximately 1.5 hours, and the mean elimination half-life of diazepam is about 49.2 hours. The recommended dose is 0.2 mg/kg or 0.3 mg/kg, depending on the patient's age and weight. Recommended doses are 5 mg, 10 mg, 15 mg, and 20 mg. The 5 mg and 10 mg doses are administered as one spray in one nostril, and the 15 mg (using two 7.5 mg devices) and 20 mg (using two 10 mg devices) doses are administered as one spray in each nostril. A second dose, when required, may be administered ≥ 4 hours after the initial dose. Do not use more than two doses of Valtoco to treat a single episode. 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. Valtoco is available in 5 mg, 7.5 mg, and 10 mg strengths; each nasal spray device contains 0.1 mL solution. Valtoco is a ready-to-use nasal spray device. Valtoco nasal spray delivers its entire contents upon activation. Do not prime or attempt to use for more than one administration per device.

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. 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. 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.

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] Based on this information, it has been estimated that more than 150,000 people in the US with uncontrolled epilepsy also experience seizure clusters.[6]

Safety

Valtoco is contraindicated in patients with acute narrow angle glaucoma or with known hypersensitivity to diazepam.[1] Similar to other benzodiazepines, Valtoco has a Boxed Warning with regard to the risk of concomitant use with opioids. Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Of note, Valtoco is not approved for use in neonates or infants because it contains the preservative benzyl alcohol. Serious and fatal adverse reactions including "gasping syndrome" can occur in neonates and low birth weight infants treated with benzyl alcohol-preserved drugs, including Valtoco.

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

15. 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)** Valtoco is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Valtoco 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. 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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66. Data on file. Clinical and economic evidence supporting formulary consideration of Nayzilam® CIV (Midazolam Nasal Spray) for seizure clusters. UCB, Inc.; June 24, 2019.

PRIOR AUTHORIZATION POLICY

POLICY: Antiepileptics – Vigabatrin (Sabril) [vigabatrin tablets and powder for solution, generics]

DATE REVIEWED: 09/18/2019; selected revision 03/25/2020

OVERVIEW

Vigabatrin is indicated as adjunctive therapy for adults and pediatric patients ≥ 2 years of age with refractory complex partial seizures who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss.[1] Vigabatrin is not indicated as a first line agent for complex partial seizures. Vigabatrin is also indicated as monotherapy for pediatric patients with infantile spasms 1 month to 2 years of age for whom the potential benefits outweigh the potential 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). In patients with infantile spasms, vigabatrin should be withdrawn if a substantial clinical benefit is not observed within 2 to 4 weeks. If, in the clinical judgment of the prescriber, evidence of treatment failure becomes obvious earlier than 2 to 4 weeks, treatment should be discontinued at that time. In a controlled clinical study in patients with infantile spasms, vigabatrin was tapered by decreasing the daily dose at a rate of 25 mg/kg to 50 mg/kg every 3 to 4 days. 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. If, in the clinical judgment of the prescriber, evidence of treatment failure becomes obvious earlier than 3 months, treatment should be discontinued at that time. In a controlled study in pediatric patients with complex partial seizures, vigabatrin was tapered by decreasing the daily dose by one third every week for 3 weeks.

The incidence of infantile spasms ranges from 2 to 3.5 per 10,000 live births and most patients present between the ages of 3 months to 7 months; 90% of patients present in the first year of life. Onset after 18 months of age is rare, although onset up to 4 years of age has been reported.[2] Infantile spasms are a catastrophic form of epilepsy in children and poor developmental outcome may result. The recommended duration therapy for Acthar is short-term (2 weeks of treatment followed by a gradual taper and discontinuation over a 2-week period).

Safety

Vigabatrin has a Boxed Warning with regard to permanent vision loss.[1] Vigabatrin can cause permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability. 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. Symptoms of vision loss from vigabatrin are unlikely to be recognized by patients or caregivers before vision loss is severe. 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. Risk of new or worsening vision loss continues as long as vigabatrin is used. 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. Under the Vigabatrin REMS Program, prescribers must be certified by enrolling in the program, agreeing to counsel patients on the risk of vision loss and the need for periodic monitoring of vision, and reporting any event suggestive of vision loss to Lundbeck. Patients must also enroll in the program, and pharmacies must be certified and must only dispense to patients authorized to receive vigabatrin.

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)** The patient is ≤ 2 years of age; AND
- **C)** Vigabatrin is being used as monotherapy; AND
- **D)** Vigabatrin 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. The patient is ≥ 2 years of age; AND
- ii. The patient has tried and/or is concomitantly receiving at least three other antiepileptic drugs; AND
- iii. Vigabatrin is prescribed by, or in consultation with, a neurologist.

Note: Examples of antiepileptic drugs include valproic acid, gabapentin, phenytoin, carbamazepine, oxcarbazepine, lacosamide, levetiracetam, zonisamide, Fycompa, lamotrigine, topiramate, rufinamide, tiagabine, felbamate, Diacomit, and clobazam.

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

Vigabatrin 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

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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.)

34. 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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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.)

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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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.)

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

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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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.)

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

66. Vfend® tablet and oral suspension [prescribing information]. New York, NY: Roerig, Division of Pfizer; January 2019.
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PRIOR AUTHORIZATION POLICY

POLICY: Antifungals (Azoles) – Intravenous Products

- Cresemba® (isavuconazonium sulfate injection, for intravenous use – Astellas Pharma, Inc)
- Fluconazole intravenous solution – multiple manufacturers
- Noxafil® (posaconazole injection for intravenous use – Merck Sharp & Dohme, a division of Merck)
- Vfend® (voriconazole for injection, for intravenous use – Roerig, a division of Pfizer; generics)

APPROVAL DATE: 02/12/2020

OVERVIEW

Cresemba (isavuconazonium) is indicated for use in patients ≥ 18 years of age for the treatment of the following fungal infections: invasive aspergillosis and invasive mucormycosis.[1] Cresemba is available as an oral capsule and a lyophilized powder to be reconstituted with Water for Injection, USP for intravenous (IV) use.

Fluconazole (Diflucan, generics) is indicated for the treatment of oropharyngeal and esophageal candidiasis and cryptococcal meningitis. Fluconazole is also indicated for prophylactic use, to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy.[2-4] In open noncomparative studies of relatively small numbers of patients, fluconazole was also effective for the treatment of *Candida* urinary tract infections, peritonitis, and systemic *Candida* infections including candidemia, disseminated candidiasis, and pneumonia. Fluconazole is available as an oral tablet, powder for oral suspension, and a solution for injection.

Noxafil (posaconazole) is indicated for the 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.[5] Noxafil oral suspension is also indicated for the treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole. Noxafil injection is indicated for use in patients ≥ 18 years of age and Noxafil delayed-release tablets and oral suspension are indicated for use in patients ≥ 13 years of age.

Voriconazole (Vfend, generics) is indicated in adults and pediatric patients (≥ 2 years of age) for the treatment of invasive aspergillosis; candidemia in non-neutropenic patients, and the following *Candida* infections: disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds; and 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.[4,6] Oral voriconazole is also indicated in adults and pediatric patients (≥ 2 years of age) for the treatment of esophageal candidiasis. Voriconazole is available as an oral tablet, powder for oral suspension, and a lyophilized powder to be reconstituted with Water for Injection, USP for IV use.[4]

Prophylactic antifungal therapies have been used to prevent invasive antifungal infections in patients at high-risk for these infections (e.g., patients who are post-allogeneic stem cell or bone marrow transplants, patients with human immunodeficiency virus [HIV] infection and low CD4 cell count, patients with myelodysplastic syndrome and/or other hematological malignancies, patients undergoing intensive immunosuppressive therapy for severe aplastic anemia).

POLICY STATEMENT

The intent of this policy is to prevent coverage of intravenous (IV) formulations of antifungals 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 topical mupirocin products. There are no data to support these uses. Prior authorization is recommended for prescription benefit coverage of Cresemba for injection, fluconazole IV solution, Noxafil for injection, and voriconazole for injection, when these products are prescribed in conjunction with topical clindamycin, topical clotrimazole, topical ketoconazole, and/or topical mupirocin products.

Automation: Prescriptions for IV Cresemba, fluconazole, Noxafil, and voriconazole without a prescription for topical clindamycin products, topical clotrimazole products, topical ketoconazole products, and topical mupirocin products in the past 180 days are excluded from the prior authorization policy. The prior authorization policy will only apply to IV Cresemba, fluconazole, Noxafil, and voriconazole with history of topical clindamycin, topical clotrimazole, topical ketoconazole, and/or topical mupirocin products in the past 180 days. When 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 is not applied in adjudication.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of IV Cresemba, fluconazole, Noxafil, and voriconazole 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

IV Cresemba, fluconazole, Noxafil, and voriconazole 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.)

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

72. Cresemba® capsule and lyophilized powder for injection [prescribing information]. Northbrook, IL: Astellas Pharma US, Inc; April 2018.
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76. 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.
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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.)

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

78. Impavido® capsules [prescribing information]. Orlando, FL: Profounda, Inc.; June 2019.
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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

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

Other Uses with Supportive Evidence

8. **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:

41. **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.

42. **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.

43. **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.

44. **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.

45. **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]

46. 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.

47. 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.

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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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)
- 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:[1-24,45,46,50-53]

- **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 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

9. **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]

49. **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]

50. **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.

51. 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]

52. 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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PRIOR AUTHORIZATION POLICY

POLICY: Bone Modifiers – Evenity™ (romosozumab-aqqg injection for subcutaneous use – Amgen)

DATE REVIEWED: 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 Indications

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.

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

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Evenity 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.)

53. Osteoporosis Prevention. Evenity is not indicated for the prevention of osteoporosis.

54. 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®).

55. 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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PRIOR AUTHORIZATION POLICY

POLICY: Bone Modifiers – Ibandronate Intravenous (Boniva IV) [Boniva® {ibandronate injection – Genentech/Roche, generics}]

DATE REVIEWED: 02/26/2020

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 cited below.

Automation: None.

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

FDA-Approved Indications

2. Osteoporosis Treatment for a Postmenopausal Patient. Approve ibandronate injection (Boniva IV) for 1 year if the patient meets the following criteria (A and B):

A) The patient meets ONE of the following conditions (i, ii, or iii):
- **iv.** 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
- **v.** The patient has had an osteoporotic fracture or a fragility fracture; OR
- **vi.** 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 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 effects); 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 in which IV bisphosphonate therapy may be warranted (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 has had an osteoporotic fracture or a fragility fracture.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Ibandronate injection (Boniva 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.)

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

57. Concurrent Use with Other Medications for Osteoporosis (e.g., other bisphosphonates [e.g., alendronate, risedronate, ibandronate], Prolia® [denosumab injection for subcutaneous use], Evenity™ [romosozumab-aqqg injection for subcutaneous use], Forteo®/Bonsity® [teriparatide injection for subcutaneous use], Tymlos® [abaloparatide injection for subcutaneous use], and calcitonin nasal spray), except calcium and Vitamin D.

58. 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; December 2016.

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:

59. 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]

60. 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]

61. Osteoporosis Prevention. Prolia is not indicated for the prevention of osteoporosis.[1]

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

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PRIOR AUTHORIZATION POLICY

POLICY: Bone Modifiers – Teriparatide Products Prior Authorization Policy

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

REVIEW DATE: 07/29/2020

OVERVIEW

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

- **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.
- **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).

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 (ASBMR) 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.

- **Postmenopausal Osteoporosis:** Teriparatide products are mentioned in guidelines for postmenopausal osteoporosis by the Endocrine Society (2019)[14] and the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) [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. However, teriparatide therapy should be limited to a duration of 2 years in a lifetime.
- **Glucocorticoid-Induced Osteoporosis (GIO):** The American College of Rheumatology (ACR) 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).

Safety

The prescribing information for teriparatide products include a Boxed Warning regarding an increased incidence of osteosarcoma in rats at doses 3 to 60 times the exposure in humans administered as a 20 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 does not recommend use of teriparatide for more than 2 years because its safety and efficacy beyond this time frame have not been evaluated.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of teriparatide products. Coverage cumulative with teriparatide products and Tymlos® (abaloparatide injection for subcutaneous use) 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. 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 are recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Glucocorticoid-Induced Osteoporosis – Treatment.** Approve for up to 2 years (total) if the patient meets the following criteria (A, B, and C):
   - **C)** Patient is either initiating or continuing systemic glucocorticoids (e.g., prednisone); AND
   - **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 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

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 (e.g., patient with esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying [stricture, achalasia]); OR

viii. 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

E) Use of teriparatide and/or Tymlos 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 Forteo, Bonsity, or Tymlos should be approved for a duration of 21 months. This allows for completion of a maximum of 2 years of therapy).

2. Osteoporosis Treatment for a Postmenopausal Patient. Approve for up to 2 years (total) 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 (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 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; AND

C) Use of teriparatide products and/or Tymlos 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 teriparatide or Tymlos should be approved for a duration of 21 months. This allows for completion of a maximum of 2 years of therapy).

3. Osteoporosis – (to Increase Bone Mass) in Men* with Primary or Hypogonadal Osteoporosis. Approve for up to 2 years (total) 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 (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 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 [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 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; AND

C) Use of teriparatide and/or Tymlos 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 teriparatide or Tymlos should be approved for a duration of 21 months. This allows for completion of a maximum of 2 years of therapy).

***** Refer to the Policy Statement.

Other Uses with Supportive Evidence

4. Hypoparathyroidism. Approve for up to 2 years (total) if the patient meets the following criteria (A and B):
1. Patient has tried Natpara (parathyroid hormone injection), or 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. The agent is prescribed by or in consultation with an endocrinologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of teriparatide is not recommended in the following situations:

63. 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).

64. 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]

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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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):
     - **v.** Patient has tried ibandronate injection (Boniva) or 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 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
     - **vii.** 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
     - **viii.** 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:

66. 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.

67. 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]

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

REFERENCES
184. Tymlos® injection for subcutaneous use [prescribing information]. Waltham, MA: Radius Health; October 2018.
185. 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.
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PRIOR AUTHORIZATION POLICY

POLICY: Bone Modifiers – Xgeva® (denosumab injection for subcutaneous use – Amgen)

DATE REVIEWED: 02/26/2020

OVERVIEW
Xgeva, a receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor, is indicated for the prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.[1] Xgeva is also 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. Xgeva is also indicated for the treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy. 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)** [e.g., Breast Cancer, Prostate Cancer, Non-Small-Cell Lung Cancer]. Approve Xgeva for 1 year if the patient meets the following criteria (A, B, C and D):
   - **A)** The patient is aged ≥ 18 years; AND
   - **B)** The agent is prescribed by, or in consultation with, a hematologist or an oncologist; AND
   - **C)** The patient has bone metastases; AND
   - **D)** Patients with prostate cancer have received at least one hormonal 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]).

2. **Multiple Myeloma (Prevention of Skeletal-Related Events).** Approve Xgeva for 1 year if the patient meets the following criteria (A and B):
   - **A)** The patient is aged ≥ 18 years; AND
   - **B)** The agent is prescribed by, or in consultation with, a hematologist or an oncologist.
3. **Giant Cell Tumor of Bone.** Approve Xgeva for 1 year.

4. **Hypercalcemia of Malignancy.** Approve Xgeva for 2 months if the patient meets the following criteria (A, B, and C):
   - **A)** The patient has a current malignancy; AND
   - **B)** The patient meets one of the following (i or ii):
     - **i.** The patient has tried intravenous (IV) bisphosphonate therapy (e.g., zoledronic acid injection [Zometa], pamidronate injection [Aredia]); OR
     - **ii.** The patient has an estimated calculated creatinine clearance (CrCl) < 30 mL/min; AND
   - **C)** The patient's albumin-corrected calcium (cCa) is ≥ 11.5 mg/dL.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Xgeva 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

67. Xgeva® injection for subcutaneous use [prescribing information]. Thousand Oaks, CA: Amgen; February 2020.
68. Prolia® injection for subcutaneous use [prescribing information]. Thousand Oaks, CA: Amgen; July 2019.

PRIOR AUTHORIZATION POLICY

POLICY: Bone Modifiers – Zoledronic Acid (Reclast) – Novartis, generics)

DATE REVIEWED: 02/26/2020

OVERVIEW

Zoldedronic acid (Reclast) is a bisphosphonate given intravenously.[1] Zoledronic acid injection (Reclast) is indicated for the treatment of osteoporosis in postmenopausal women; for the prevention of postmenopausal osteoporosis (PMO) in women; the treatment of Paget's disease of bone in men and women; for the treatment to increase bone mass in men with osteoporosis; and for the treatment and prevention of glucocorticoid-induced osteoporosis (GIO) in patients expected to be on systemic glucocorticoids (daily dosage equivalent to ≥ 7.5 mg of prednisone) for at least 12 months.[1] In PMO, zoledronic acid injection (Reclast) reduces the incidence of fractures (hip, vertebral and non-vertebral osteoporosis-related fractures). Also, for patients at high risk of fracture, defined as a recent low-trauma hip fracture, zoledronic acid injection (Reclast) reduces the incidence of new clinical fractures.[1] Another zoledronic acid injection product, Zometa®, is indicated for hypercalcemia of malignancy; and for multiple myeloma and bone metastases from solid tumors.[2]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of zoledronic acid injection (Reclast). All approvals are provided for the duration cited 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. **Osteoporosis Treatment for a Postmenopausal Patient.** Approve 1 year if the patient meets the following criteria (A and B):
   - **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 is at high risk for fracture; AND
   - **B)** The patient meets ONE of the following (i, ii, iii, or iv):
     - **i.** The patient has tried 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 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 GI-related adverse effects); 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 GI medical condition in which IV bisphosphonate therapy may be warranted (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 has had an osteoporotic fracture or a fragility fracture.

2. Osteoporosis Treatment for Men*. Approve for 1 year if the patient meets the following criteria (A and B):

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 is at high risk for fracture; AND

B) The patient meets ONE of the following (i, ii, iii, or iv):
- **i.** The patient has tried 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 effects); 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 in which IV bisphosphonate therapy may be warranted (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 zoledronic acid injection (Reclast); OR
- **iv.** The patient has had an osteoporotic fracture or a fragility fracture.

***** Refer to the Policy Statement.

3. Glucocorticoid-Induced Osteoporosis (GIO) Prevention and Treatment. Approve for 1 year if the patient meets the following criteria (A and B):

A) The patient is either initiating or continuing systemic glucocorticoids (e.g., prednisone); AND

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

i. The patient has tried 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 fragility fracture while receiving oral bisphosphonate therapy; OR
  c) The patient has experienced intolerability to an oral bisphosphonate (e.g., severe GI-related adverse effects); 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 in which IV bisphosphonate therapy may be warranted (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 zoledronic acid injection (Reclast); OR

iv. The patient has had an osteoporotic fracture or a fragility fracture.

4. Paget's Disease of the Bone. Approve for one dose if the patient meets ONE of the following criteria (A, B, or C):

A) The patient has elevations in serum alkaline phosphatase of two times higher than the upper limit of the age-specific normal reference range; OR

B) The patient is symptomatic (e.g., bone pain, hearing loss, osteoarthritis); OR

C) The patient is at risk for complications from their disease (e.g., immobilization, bone deformity, fractures, nerve compression syndrome).

5. Osteoporosis Prevention 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 or ii):
  i. The 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. The patient has had an osteoporotic fracture or a fragility fracture; AND

B) The patient meets ONE of the following (i, ii, iii, or iv):
  i. The patient has tried 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 BMD, lack of BMD increase); OR
    b) The patient has had an osteoporotic fracture or 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 effects); 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 in which IV bisphosphonate therapy may be warranted (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 zoledronic acid injection (Reclast); OR

iv. The patient has had an osteoporotic fracture or a fragility fracture.

C) If the patient has received Reclast previously, at least 24 months has elapsed since the last dose.

Other Uses with Supportive Evidence

6. Osteogenesis Imperfecta. Approve zoledronic acid injection (Reclast) for 1 year.

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]

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Zoldedronic acid (Reclast) 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 Other Medications for Osteoporosis (e.g., other bisphosphonates [e.g., alendronate, risedronate, ibandronate], Prolia® [denosumab injection for subcutaneous use], Evenity™ [romosozumab-aqqg injection for subcutaneous use], Forteo/Bonsity® [teriparatide injection for subcutaneous use], Tymlos® [abaloparatide injection for subcutaneous use], and calcitonin nasal spray), except calcium and Vitamin D.

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

2. Reclast® injection [prescribing information]. East Hanover, NJ: Novartis; July 2017.
3. Zometa® injection for intravenous infusion [prescribing information]. East Hanover, NJ: Novartis; December 2018.
4. Biggin A, Munns CF. Long-term bisphosphonate therapy in osteogenesis imperfecta. *Curr Osteoporos Rep*. 2017;15(5):412-418.
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6. 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.
7. Brown JJ, Zacharin MR. Safety and efficacy of intravenous zoledronic acid in paediatric osteoporosis. *J Pediatr Endocrinol Metab*. 2009;22(1):55-63.
8. Vuorimies I, Toiviainen-Salo S, Hero M, Makitie O. Zoledronic acid treatment in children with osteogenesis imperfecta. *Horm Res Paediatr*. 2011;75:346-353.
9. Dwan K, Phillipi CA, Steiner RD, Basel D. Bisphosphonate therapy for osteogenesis imperfecta. *Cochrane Database Syst Rev*. 2016;10:CD005088.

POLICY: Zoledronic Acid (Zometa® [zoledronic acid injection] – Novartis, generics)

DATE REVIEWED: 02/26/2020

OVERVIEW

Zoledronic acid injection (Zometa) is indicated for the treatment of hypercalcemia of malignancy, defined as an albumin-corrected calcium (cCa) ≥ 12 mg/dL (3.0 mmol/L). Zoledronic acid injection (Zometa) is also indicated for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. A limitation of use is that the efficacy and safety of zoledronic acid injection (Zometa) in the treatment of hypercalcemia associated with hyperparathyroidism or with other nontumor-related conditions have not been established. 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 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 preventing and treatment 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) also has 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 4.2019 – August 19, 2019)[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

16. **Hypercalcemia of Malignancy.** Approve for 1 month if the patient meets the following criteria (A and B):
    - **A)** The patient has a current malignancy; AND
    - **B)** The patient's albumin-corrected calcium (cCa) is ≥ 11.5 mg/dL.

17. **Multiple Myeloma (Treatment).** Approve for 1 year if the agent is prescribed by or in consultation with a hematologist or oncologist.

18. **Treatment of Bone Metastases From Solid Tumors** (e.g., Breast Cancer, Prostate Cancer, Non-Small Cell Lung Cancer, Renal Cell Cancer, Small Cell Lung Cancer, Colorectal Cancer, Bladder Cancer, Gastrointestinal/Genitourinary Cancer, Head and Neck Cancer). Approve for 1 year if the patients meets all of the following criteria (A, B, and C):
    - **A)** The agent must be prescribed by or in consultation with a hematologist or oncologist; AND
    - **B)** The patient has bone metastases; AND
    - **C)** Patients with prostate cancer have received at least one hormonal 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]).

Other Uses with Supportive Evidence

19. **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)** The patient has breast cancer that is not metastatic to bone; AND
    - **B)** The patient is receiving an aromatase inhibitor therapy (e.g., anastrozole, letrozole, and exemestane).

20. **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)** The patient has prostate cancer that is not metastatic to bone; AND
    - **B)** The patient is currently 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 the patient has undergone bilateral orchiectomy.

21. 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 and B):
A) The patient is a premenopausal patient with breast cancer that is not metastatic to bone; AND
B) The patient has received adjuvant chemotherapy and has developed ovarian failure.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Zoledronic acid IV (Zometa) 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.

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PRIOR AUTHORIZATION POLICY

POLICY: Botulinum Toxins – Botox® (onabotulinumtoxinA for injection – Allergan)

DATE REVIEWED: 06/03/2020

OVERVIEW

Botox® (onabotulinumtoxinA), 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;
- lower limb spasticity in adults to decrease the severity of increased muscle tone in ankle and toe flexors;
- lower limb spasticity in pediatric patients 2 to 17 years of age, excluding spasticity caused by cerebral palsy;
- upper limb spasticity in adults to decrease the severity of increased muscle tone in elbow flexors, wrist flexors, finger flexors, and thumb flexors;
- upper limb spasticity in pediatric patients 2 to 17 years of age; AND
- 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.[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]

Botox® Cosmetic (onabotulinumtoxinA) is indicated for the temporary improvement in appearance of moderate to severe glabellar lines with corrugator and/or procerus muscle activity in adults, moderate to severe lateral canthal lines associated with orbicularis oculi activity in adults, and moderate to severe forehead lines associated with frontalis muscle activity.[4] Botox Cosmetic is not included in this policy.

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® (incobotulinumtoxinA), 1:3 for Botox to Dysport® (abobotulinumtoxinA), and 1:50 to 1:100 for Botox to Myobloc® (rimabotulinumtoxinB) have been suggested.[5,6]

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 clinical data on the use of botulinum toxin A for treatment of achalasia are extensive and suggest that it is effective in the majority of patients treated; 70% to 100% of patients experience short-term symptomatic relief.[7,8] A large amount of data from both uncontrolled studies and randomized, controlled studies support the effectiveness of botulinum toxin A as a non-invasive therapeutic alternative.[9-11] 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).[12]
- **Anal Fissures:** 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.[7,13-15] The majority of the available data are evaluating use of Botox. Overall, injections of botulinum toxin A have resulted in healing of 60% to 80% of anal fissures.[16] Botulinum toxin A appears to be a safe and effective short-term treatment of chronic anal fissure, demonstrating a healing rate of 70% to 98% after 2 to 4 months.[17] Botox has been shown to be more effective than topical nitroglycerin but less effective than surgery in inducing and maintaining fissure healing. 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.[14]

- **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.[18-21]
- **Chronic Low Back Pain (CLBP):** In one 8-week, randomized, double-blind, placebo-controlled trial in 31 patients with CLBP (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.[22] 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 CLBP. A total of 53% and 52% of patients reported significant pain relief at 3 weeks and 2 months, respectively.[23]
- **Dystonia, other than cervical (e.g., focal dystonias, tardive dystonia, anismus, laryngeal dystonia/spasmodic dysphonia):** In one large, prospective, 5-year, open-label study in 477 patients with various focal dystonias (symptomatic despite optimum pharmacological or surgical therapy), 93% of patients reported moderate to marked relief of their spasm after treatment with Botox.[24] Data from several other smaller open-label studies, case reports, and small, randomized, controlled trials further support the effectiveness of Botox in the treatment of non-cervical dystonias.[25-30] 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).[31] 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.[32] 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).[31]
- **Essential Tremor:** According to the clinical practice parameter on essential tremor (ET) by the American Academy of Neurology, propranolol and primidone are first-line therapy in the treatment of essential tremor.[33] Second-line medication options include alprazolam, atenolol, (monotherapy), sotalol, gabapentin, and topirimate. 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 ET (Level C for limb, head, and voice tremor). Botox was shown to significantly improve tremor severity and postural tremor outcomes compared with placebo in two randomized, double-blind, placebo-controlled studies in a total of 158 patients with moderate to severe essential hand tremor.[34,35] Open-label studies as well as one double-blind, placebo-controlled study support the effectiveness of botulinum toxin A in improving essential voice tremor and essential head tremor (head tremor without dystonia).[36-38]
- **Frey's Syndrome (gustatory sweating):** Botulinum toxin A has been shown to be highly effective in treating the symptoms (i.e., hyperhidrosis and facial flushing) of Frey's syndrome and has emerged as the treatment of choice in the treatment of this condition.[39-41] In six open-label trials in a total of 132 patients with Frey's syndrome/gustatory sweating, injections of Botox resulted in the complete absence or pronounced improvement of symptoms in all patients studied.[40-46] Although AAN guidelines only 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.[47,48]

- **Hyperhidrosis, Palmar/Plantar and Facial:** Overall, topical antiperspirants (e.g., aluminum chloride) are the recommended first-line therapy for the treatment of primary focal hyperhidrosis; other conventional treatments include oral anticholinergics.[8,49-51] Topical treatment is more effective in mild cases compared with more severe cases.[39] 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.[3,8,39] Guidelines from the International Hyperhidrosis Society support use of Botox in patients who have failed to respond to topical therapy.[47,52,53] 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).[48]
- **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.[18,54] 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.[55] 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.[56]
- **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.[57] 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.[58,59] Data from uncontrolled studies have shown Botox to be beneficial in the treatment of sixth nerve palsy.[60,61]
- **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.[62] 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].[63]
- **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).[64] AAN guidelines note that botulinum toxin is probably safe and effective and should be considered (Level B).[48]
- **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):** Botulinum toxin is the most widely used treatment for focal spasticity.[65] Neurosurgery and 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.[66] Several randomized, double-blind, placebo-controlled trials support the effectiveness of botulinum toxin A in the treatment of focal spasticity/focal hypertonia.[18,67-71] 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.[72] The majority of the data evaluated the use of Botox. 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.[73] In an observational study, patients (n = 133) with hemifacial spasm or reinnervation synkinesias were exclusively treated with either Botox or Dysport for 6 years (range, 2 to 12 years) with a minimum of eight consecutive treatments.[74] The therapeutic effect was stable throughout observation in 85% of patients. There were no differences between both drugs with respect to efficacy or safety. 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).[31,75]

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 ESI 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., β-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 (e.g., oral anticholinergic medication [for example: oxybutynin, tolterodine tartrate, trospium chloride, Enablex, Toviaz, Vesicare] or Myrbetriq).
   (Note: For treatment of urinary incontinence associated with a neurological condition [e.g., spinal cord injury, multiple sclerosis], 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).** Approve for 1 year if the patient has tried at least one other pharmacologic therapy (e.g., an anticholinergic medication [for example: oxybutynin, tolterodine tartrate, trospium chloride, Enablex, Toviaz, Vesicare] or Myrbetriq).
   (Note: 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

Botox 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 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.

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.[76] 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).[13] 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.[77]

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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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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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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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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PRIOR AUTHORIZATION POLICY

POLICY: Bupropion

- Aplenzin® (buproprion hydrobromide extended-release tablets – Valeant/sanofi-aventis)
- Forfivo™ XL (bupropion/budeprion hydrochloride extended-release tablets – Pillar5/Edgemont)
- Wellbutrin SR® (bupropion/budeprion hydrochloride sustained-release tablets – GlaxoSmithKline; generics)
- Wellbutrin XL® (bupropion/budeprion hydrochloride extended-release tablets – Biovail/BTA Pharmaceuticals, generics)

APPROVAL DATE: 11/13/2013; selected revision 08/06/2014

LAY CRITERIA EFFECTIVE DATE: 08/26/2014

OVERVIEW

Bupropion hydrochloride sustained- and extended-release (Wellbutrin SR, Wellbutrin XL, generics, Forfivo XL), and bupropion hydrobromide extended-release (Aplenzin) are indicated for the treatment of major depressive disorder (MDD).[1-3,13] Bupropion hydrochloride extended-release and Aplenzin are also indicated for the prevention of seasonal major depressive episodes in patients diagnosed with seasonal affective disorder. Bupropion has also been used for treatment of other conditions such as attention deficit hyperactivity disorder (ADHD).[4]

Smoking Cessation

Another bupropion hydrochloride sustained-release product, Zyban®, is indicated as an aid to smoking cessation treatment.[5] Forfivo XL, Wellbutrin/SR/XL and Zyban, and their generics, contain the same active ingredient, bupropion hydrochloride. While Aplenzin contains bupropion hydrobromide, it is bioequivalent to Wellbutrin XL.[3]

Weight Loss

Weight gain may be a side effect of antidepressant drug therapy and may contribute to patient dissatisfaction with treatment and noncompliance. Some antidepressant drugs are more likely than others to cause weight gain. In short-term (8-week) placebo-controlled trials where bupropion sustained-release (SR) was used to treat depression, weight loss of greater than 5 pounds (lbs) occurred in 14% to 19% of patients on bupropion vs. 6% of placebo patients.[1] Patients who lost greater than 10 lbs were above ideal body weight. In three placebo-controlled trials of seasonal affective disorder with bupropion extended-release (XL), weight loss of > 5 lbs occurred in 23% of patients on bupropion vs. 11% of placebo patients; 11% of patients on bupropion gained > 5 lbs vs. 21% of placebo patients.[2]

In a 52-week study in adults with recurrent major depression, modest mean weight losses that increased with increasing baseline body weight were observed with bupropion SR treatment (i.e., with baseline body

mass index [BMI] ≥ 30 kg/m^2, mean decrease was 2.4 kg vs. 1.4 kg with BMI ≥ 27).[6] In smoking cessation studies (7 to 9 weeks) weight gain was less during treatment with bupropion SR compared with placebo.[7-8] In long-term maintenance for smoking cessation, patients who continued with bupropion SR for up to 52 weeks gained less weight than patients who were on placebo.[9]

In a 26-week, double-blind study, obese adults (BMI 30 to 44 kg/m^2) who were not currently diagnosed with MDD but who had depressive symptoms were randomized to bupropion SR 150 mg twice daily or placebo with a 500 kcal/day deficit diet.[10] About 25% of patients had a history of MDD. Patients who lost < 5% of their baseline weight at Week 12 had the bupropion SR dosage or placebo increased to 400 mg/day. Approximately one-half of the patients completed the study, 121 in the bupropion SR group (57% of those randomized) and 108 in the placebo group (52% of randomized patients). Patients on bupropion SR (n = 193) lost an average of 4.4 kg (4.6% of baseline weight) vs. 1.7 kg (1.8% of baseline weight) on placebo (n = 191) [P < 0.001, last observation carried forward {LOCF} analysis]. The percentage of patients who lost ≥ 5% of baseline weight was significantly greater with bupropion SR than with placebo (P < 0.05 at Week 4; P < 0.001 for the remaining weeks). In the intent-to-treat (ITT) group, 40% of patients on bupropion SR vs. 16% on placebo lost ≥ 5% of their baseline weight by Week 26 (P < 0.001).

Bupropion SR has also been effective for weight loss in obese, non-depressed patients.[11-12] In a 48-week study, obese patients (BMI 30 to 44 kg/m^2) who completed 24 weeks of the study, lost 5%, 7.2%, and 10.1% of their initial body weight with placebo, bupropion SR 300 mg/day, and bupropion SR 400 mg/day, respectively.[12] In those who completed 48 weeks of therapy, weight loss was sustained with bupropion SR (respective mean losses of initial body weight were 7.5% and 8.6% for 300 and 400 mg, respectively).

POLICY STATEMENT

Prescription benefit coverage of Aplenzin, Forfivo XL, Wellbutrin, Wellbutrin SR, and Wellbutrin XL or their generics for use in smoking cessation or weight loss treatment should be determined by the member's benefit for smoking cessation or weight loss products. Therefore, prior authorization is recommended for prescription benefit coverage of bupropion/budeprion hydrochloride sustained-release and extended-release tablets (Forfivo XL, Wellbutrin SR, Wellbutrin XL, and their generics) and bupropion hydrobromide extended-release tablets (Aplenzin) to appropriately limit the coverage of these products to use in conditions other than smoking cessation or weight loss treatment (e.g., depression, ADHD) in order to manage the prescription pharmacy benefit. All approvals are provided for 3 years in duration unless otherwise noted below.

Automation: If criteria for previous use of an antidepressant medication (automated) are not met at the point of service, coverage will be determined by prior authorization criteria.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Aplenzin, Forfivo XL, Wellbutrin SR, Wellbutrin XL or their generics is recommended in those who meet the following criteria:

Food and Drug Administration (FDA)-Approved Indications

1. **Indications Other than Smoking Cessation (or to prevent relapse after successfully stopping smoking) or Weight Loss or Prevention of Weight Gain.** Approve.

   Bupropion is indicated for the treatment of major depressive disorder. Bupropion has been used for many off-label indications. Bupropion is not indicated for weight loss.

EXCLUSIONS

Coverage of Aplenzin, Forfivo XL, Wellbutrin SR, Wellbutrin XL or their generics is recommended in circumstances that are listed in the Recommended Authorization Criteria (FDA-Approved Indications and Other Uses with Supportive Evidence). The following provides rationale for specific Exclusions. This is not an exhaustive list of Exclusions.

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria.

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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

10. Migraine Headache Prevention. Approve Aimovig for 1 year if the patient meets the following criteria (A, B, C, and D):

4. Patient is ≥ 18 years of age; AND

5. Patient has ≥ 4 migraine headache days per month (prior to initiating a migraine-preventative medication); AND

6. 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

7. 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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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

11. Migraine Headache Prevention. Approve Ajovy for 1 year if the patient meets the following criteria (A, B, C, and D):
- **8.** Patient is ≥ 18 years of age; AND
- **9.** Patient has ≥ 4 migraine headache days per month (prior to initiating a migraine-preventative medication); AND
- **10.** 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
- **11.** 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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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

12. Episodic Cluster Headache Treatment. Approve Emgality for 6 months if the patient meets the following criteria (A, B, C, and D):
- **12.** Patient is ≥ 18 years of age; AND
- **13.** Patient has between one headache every other day and eight headaches per day; AND
- **14.** 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.
- **15.** 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.

13. 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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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

14. Migraine Headache Prevention. Approve Vyepti for 1 year if the patient meets the following criteria (A, B, C, and D):

16. Patient is ≥ 18 years of age; AND

17. Patient has ≥ 4 migraine headache days per month (prior to initiating a migraine-preventative medication); AND

18. 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

19. 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.)

14. Acute Treatment of Migraine. Clinical data is currently lacking for the use of Vyepti in the acute treatment of migraine.

15. 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]

16. 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]

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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PRIOR AUTHORIZATION POLICY

POLICY: Cardiology – Corlanor® (ivabradine tablets and oral solution – Amgen)

DATE REVIEWED: 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 1 year in duration.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

15. 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

Corlanor 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.)

69. 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]

70. 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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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-dimercaptosuccininc 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.

71. **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]

72. **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]

73. **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).

74. 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.

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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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):

20. 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.

21. 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.)

76. 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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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.

REFERENCES

132. Cuprimine® [prescribing information]. Bridgewater, NJ. Aton Pharma. Inc., a division of Valeant Pharmaceuticals North America LLC; November 2019.
133. Depen® [prescribing information]. Somerset, NJ. Meda Pharmaceuticals Inc.; January 2019.
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PRIOR AUTHORIZATION POLICY

POLICY: Chelating Agents – Syprine® (trientine hydrochloride capsules – Valeant, generics)

TAC APPROVAL DATE: 09/18/2019

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 (RA), 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 (AEs). 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 (Syprine, generics). Because of the specialized skills required for evaluation and diagnosis of patients treated with trientine (Syprine, generics) as well as the monitoring required for AEs and long-term efficacy, initial approval requires trientine (Syprine, generics) 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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of trientine (Syprine, generics) is recommended in those who meet the following criteria:

FDA-Approved Indications

4. Wilson's Disease. Approve trientine (Syprine, generics) for 3 years if the patient meets the following criteria (A and B):
- **D)** The medication is prescribed by or in consultation with a gastroenterologist, hepatologist, or liver transplant physician; AND
- **E)** The patient meets ONE of the following criteria (i, ii, iii, iv, v or vi):
  - **i.** The patient has tried one penicillamine product and according to the prescriber is intolerant to penicillamine therapy; OR
    NOTE: Examples of penicillamine products are Cuprimine® (penicillamine capsules, generics), Depen® (penicillamine tablets).
  - **ii.** According to the prescriber, the patient has clinical features indicating the potential for intolerance to penicillamine therapy; OR
    NOTE: Specific clinical features include history of any renal disease, congestive splenomegaly causing severe thrombocytopenia, autoimmune tendency.
  - **iii.** According to the prescriber, the patient has a contraindication to penicillamine therapy; OR
  - **iv.** The patient has neurologic manifestations of Wilson's disease; OR
  - **v.** The patient is pregnant; OR
  - **vi.** The patient has been started on therapy with trientine (Syprine, generics).

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Trientine (Syprine, generics) 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.)

77. Biliary Cirrhosis: Trientine (Syprine, generics) is not indicated for the treatment of biliary cirrhosis.[1]

78. 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.

79. 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.

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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137. Syprine® [prescribing information]. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC; December 2016.
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139. Roberts EA, Schilsky MI. AASLD Practice Guidelines: Diagnosis and treatment of Wilson Disease: an update. *Hepatology*. 2008;47(6):2089-2111.
140. European Association for Study of the Liver (EASL) clinical practice guidelines: Wilson's disease. *J Hepatol*. 2012;56(3):671-85.
141. Cuprimine® [prescribing information]. Bridgewater, NJ. Aton Pharma. Inc., a division of Valeant Pharmaceuticals North America LLC; March 2018.
142. Depen® [prescribing information]. Somerset, NJ. Meda Pharmaceuticals Inc.; January 2019.

OTHER REFERENCES UTILIZED

- Socha P, Janczyk W, Dhawan A, et al. Wilson's disease in children: a position paper by the hepatology committee of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr*. 2018;66(2):334-344.

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:

18. **Combination Therapy with Cholbam™** (cholic acid capsules). There are no efficacy data available to support use of combination therapy with Chenodal and Cholbam.

19. 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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PRIOR AUTHORIZATION POLICY

POLICY: Cholbam® (cholic acid capsules – Retrophin)

REVIEW DATE: 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.)

81. Combination Therapy with Chenodal. There are no efficacy data available to support use of combination therapy with Cholbam and Chenodal.

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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PRIOR AUTHORIZATION POLICY

POLICY: Cinacalcet tablets (Sensipar® – Amgen, Inc.)

REVIEW DATE: 02/12/2020; Selected revision, 3/11/2020

OVERVIEW

Cinacalcet (Sensipar, generics) is a calcium-sensing receptor agonist (calcimimetic) indicated for the treatment of secondary hyperparathyroidism in adult patients with chronic kidney disease (CKD) on dialysis.[1] Cinacalcet is also indicated for the treatment of hypercalcemia in adult patients with parathyroid carcinoma and for the treatment of 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.

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 an uncommon cause of primary hyperparathyroidism.[3] It 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) recommends 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. 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. All approvals are provided for 1 year in duration unless otherwise noted below.

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. 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)** Cinacalcet is prescribed by, or in consultation with, a nephrologist or endocrinologist.

22. Hypercalcemia due to Parathyroid Carcinoma. Approve for 1 year if cinacalcet is prescribed by, or in consultation with, an oncologist or endocrinologist.

23. 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 parathyroidectomy due to a contraindication; AND
- **B)** Cinacalcet 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)** Cinacalcet is prescribed by, or in consultation with, a transplant physician, nephrologist, or endocrinologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Sensipar 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.)

83. Patients with Primary Hyperparathyroidism eligible for Parathyroidectomy. Parathyroidectomy is the primary treatment for primary hyperparathyroidism.

84. 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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243. Kidney Disease Improving Global Outcomes (KDIGO). KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). © 2017 KDIGO. Available at: http://www.kdigo.org/pdf/KDIGO%20CKD-MBD%20GL%20KI%20Suppl%20113.pdf. Accessed on February 6, 2020.

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:

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. 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.
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12. Mitsuyasu R. Prevention of bacterial infections in patients with advanced HIV infection. *AIDS*. 1999;13(Suppl 2):S19-S23.
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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.

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:

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
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.

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

22. **Acute Myeloid Leukemia.** Approve for 6 months if the patient is prescribed by or in consultation with an oncologist or a hematologist.

23. **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.

24. **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.

25. **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

26. **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:

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
96. Leukine® injection for intravenous or subcutaneous use [prescribing information]. Lexington, MA: Partner Therapeutics; May 2018.
97. Unituxin™ injection for intravenous use [prescribing information]. Silver Springs, MD: United Therapeutic Corporation; March 2017.

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.

27. 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

28. 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:

23. 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]

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

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.
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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.

PRIOR AUTHORIZATION POLICY

POLICY: Complement Inhibitors – Ultomiris™ (ravulizumab-cwvz injection for intravenous use – Alexion)

REVIEW DATE: 11/06/2019

OVERVIEW

Ultomiris is a complement inhibitor indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) and for the treatment of adults and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).[1] 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 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. 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 intravenous (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

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 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. 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.

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.

Safety

Ultomiris has a Boxed Warning regarding life-threatening and fatal meningococcal infections.[1] Meningococcal infections have occurred in patients receiving Ultomiris and may become rapidly life-threatening or fatal if not

recognized and treated early. Ultomiris is contraindicated in patients with unresolved serious *Neisseria meningitidis* infection. Ultomiris has a Risk Evaluation and Mitigation Strategy (REMS) program to mitigate the occurrence and morbidity associated with meningococcal infections. The REMS program also educates healthcare professionals and patients regarding the increased risk of meningococcal infections with Ultomiris, the early signs of invasive meningococcal infections, and the need for immediate medical evaluation of signs and symptoms consistent with possible meningococcal infections.

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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

25. Paroxysmal Nocturnal Hemoglobinuria. Approve Ultomiris for the duration noted if the patient meets ONE of the following (A or B):
- **A)** 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.** PNH 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
- **B)** Patient currently receiving Ultomiris: Approve Ultomiris for 1 year if the patient is continuing to derive benefit (e.g., stabilization of hemoglobin levels, decreased transfusion requirements or transfusion independence, reductions in hemolysis) from Ultomiris, according to the prescribing physician.

26. Atypical Hemolytic Uremic Syndrome. Approve Ultomiris 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

Ultomiris 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.)

25. 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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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

85. **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.

86. **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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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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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

27. 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

28. 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.)

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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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.)

87. **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.

88. **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]

89. 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.

90. 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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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

29. 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.)

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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PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis – Kalydeco® (ivacaftor tablets and oral granules – Vertex)

REVIEW DATE: 03/25/2020

OVERVIEW

Kalydeco, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, is indicated for the treatment of cystic fibrosis (CF) in patients ≥ 6 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. Mutations with an increase in chloride transport of 10% or greater are considered responsive.[1] 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.[1] 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]

E56K	*G178R*	*S549R*	*K1060T*	*G1244E*
P67L	*E193K*	*G551D*	*A1067T*	*S1251N*
R74W	*L206W*	*G551S*	*G1069R*	*S1255P*
D110E	*R347H*	*D579G*	*R1070Q*	*D1270N*
D11OH	*R352Q*	*S945L*	*R1070W*	*G1349D*
R117C	*A455E*	*S977F*	*F1074L*	*2789+5G—>A*
R117H	*S549N*	*F1052V*	*D1152H*	*3272-26A—>G*
3849+10kbC—>T	*711+3A—>G*	*E831X*		

CFTR – Cystic fibrosis transmembrane regulator.

Disease Overview

The CFTR protein is a chloride channel present at the surface of epithelial cells in multiple organs. Kalydeco facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein.[1] More than 1,800 disease-associated changes or mutations have been identified in the CFTR gene.[2] According to the CF patient registry (2018) about 44.2% of patients have two copies of the F508del (Delta F508) mutation; about 40.5% of patients with CF have one F508del mutation; 15.3% of patients do not have an F508del mutation or it is unknown if they have such a mutation.[2,5]

Guidelines

Guidelines from the CF Foundation (2018) provide guidance on the use of CFTR therapy in patients with CF.[3] For patients ≥ 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 make 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 patients with R117H mutation, the Guidelines recommend against treatment with Kalydeco for children 12 to 17 years of age with ppFEV1 > 90% and in children < 6 years of age. Among patients who are homozygous for F508del, the guidelines make a strong recommendation for treatment with Orkambi (lumacaftor/ivacaftor tablets and oral granules) in adults and children ≥ 12 years of age with ppFEV1 < 90%; and make a conditional recommendation for treatment with Orkambi in adults and children ≥ 12 years of age with ppFEV1 > 90% and for children 6 to 11 years of age.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Kalydeco. 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. All approvals are provided for 3 years unless otherwise noted below.

Automation: None

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

22. Cystic Fibrosis (CF). Approve Kalydeco for 3 years in patients who meet the following criteria A, B, and C:

A) The 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, OR R117H; AND

B) The patient is ≥ 6 months of age; AND

C) Kalydeco is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic CF.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Kalydeco 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. 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.[4]

92. Cystic Fibrosis (CF), Patients with Unknown Cystic Fibrosis Transmembrane Regulator (CFTR) Gene Mutation. A Food and Drug Administration (FDA)-cleared CF mutation test should be used to detect the presence of the CFTR mutation prior to use of Kalydeco.[1]

93. 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.

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PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis – Orkambi™ (lumacaftor/ivacaftor tablets and oral granules – Vertex)

REVIEW DATE: 07/10/2019; selected revision 10/23/2019

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.

In patients with CF, mutations in both copies of the cystic fibrosis transmembrane conductance regulator (CFTR) gene disrupt normal production of the CFTR protein.[3] Different mutations cause CFTR to malfunction in different ways. In some people with CF, little to no CFTR is produced. In others, the defective protein is produced, but cannot move to the surface of the cell where it is needed to regulate the transfer of chloride and water in and out of cells. In others CFTR is produced and moves to the surface of the cell, but the gate that controls chloride movement does not open properly. The malfunctioning CFTR leads to an accumulation of unusually thick and stick mucus in the lungs, pancreas, and other organs. As new therapies are developed, it is very important for individuals to know which mutations are present. There are > 1,800 known CFTR mutations, many of which have been categorized into different groups. People with two mutations in classes I, II, and III typically exhibit more severe pulmonary disease and pancreatic insufficiency as compared to people with at least one mutation in classes IV and V. The F508del mutation is considered a class II mutation. Class II mutations are those in which the CFTR protein is created, but misfolded, keeping it from reaching the cell surface. According to the CF patient registry about 45.3% of patients have two copies of the F508del (Delta F508) mutation; about 40.9% of patients with CF have one F508del mutation; 13.7% of patients do not have an F508del mutation or it is unknown if they have such a mutation.[2]

The efficacy of Orkambi was established in two Phase III, randomized, double-blind, placebo-controlled, multicenter, pivotal studies in patients ≥ 12 years of age with CF who were homozygous for the F508del mutation in the CFTR gene.[3] In both studies, Orkambi was compared with placebo, as well as a different dose of the components contained within Orkambi (lumacaftor 600 mg once daily [QD] + ivacaftor 250 mg Q12H). The primary endpoint for both studies was the absolute change from baseline at Week 24 in the % of predicted forced expiratory volume in 1 second (FEV1), calculated by averaging the mean absolute change at Week 16 and the mean absolute change at Week 24. In TRAFFIC (n = 549), the mean absolute change (improvement) from baseline in FEV1 % predicted at 24 weeks in patients treated with Orkambi was 2.6% ($P < 0.001$ vs. placebo). In TRANSPORT (n = 599), the mean absolute change (improvement) from baseline in FEV1 % predicted at 24 weeks in patients treated with Orkambi was 3.0% ($P < 0.001$ vs. placebo).

The efficacy of Orkambi in children 6 through 11 years of age is extrapolated from efficacy in patients ≥ 12 years of age homozygous for the *F508del* mutation in the *CFTR* gene with support from population pharmacokinetic analyses showing similar drug exposure levels in patients ages 12 years and older and in children ages 6 through 11 years.[1] Additional safety data were obtained from a 24-week, open-label, Phase 3 clinical trial in 58 patients aged 6 through 11 years, mean age 9 years (unpublished). This study evaluated subjects with a screening FEV_1 ≥40 (mean ppFEV1 91.4 at baseline [range: 55 to 122.7]). The safety profile of Orkambi in children 6 through 11 years of age was similar to those in patients ≥ 12 years of age. Spirometry was assessed as a planned safety endpoint. The within-group LS mean absolute change from baseline in FEV_1 at Week 24 was 2.5 percentage points. At the Week 26 safety follow-up visit (following a planned discontinuation) $FEV_1$was also assessed. The within-group LS mean absolute change in FEV1 from Week 24 at Week 26 was -3.2 percentage points.

Guidelines

Guidelines from the CF Foundation (January 2018) provide guidance on the use of CFTR therapy in patients with CF.[4] The Guideline is not intended to establish a standard of care, rather it is intended to represent an effort to summarize evidence and provide sensible clinical recommendations based on the evidence. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the evidence and develop recommendations. The Committee did not choose to evaluate the clinical situations for which recommendations have already been published (e.g., Kalydeco for patients ≥ 12 years of age who carry at least one copy of the G551D mutation or CF patients 2 to 5 years of age with gating mutations other than G551D, or if the issue was of low priority and unlikely to change clinical practice (e.g., Orkambi in patients homozygous for F508del). Data for consideration were collected through April 2016. Recommendations are provided below.

The recommendations for Orkambi vs. no CFTR modulator therapy in patients homozygous for F508del are presented in Table 1 below. The recommendations for these patients place a high value on the potential improvement of patient-important outcomes, such as lung function. There is an abundance of data from clinical trials that demonstrates significant clinical improvement in patient-important outcomes for patients' ≥ 12 years of age with baseline $ppFEV_1 \leq 90\%$ treated with Orkambi. For this reason, the Committee made a strong recommendation for treatment with moderate certainty in the evidence. Patients with baseline $ppFEV_1 > 90\%$ failed to demonstrate equivalent improvements but the ability of the Committee to draw conclusions was hindered a by small numbers of patients in this lung function cohort. Nonetheless, the Committee concluded that the potential for preservation of lung function and other outcomes justified a conditional recommendation in favor of treatment. Another consideration in the decision to prescribe Orkambi is the reported increased incidence of cough and chest tightness among patients of all ages with $ppFEV_1 < 40\%$. Patients have generally tolerated gradual reintroduction of therapy but early worsening of symptoms should be included in treatment discussions.

Table 1. CFF Recommendations for Orkambi in Patients Homozygous for F508del Mutation.[4]

Age	ppFEV$_1$	Certainty	Recommendation
0 to 5 years	N/A	N/A	No Recommendation
6 to 11 years	< 40%	Very Low	Conditional For
	40% to 90%	Very Low	Conditional For
	> 90%	Very Low	Conditional For
12 to 17 years	< 40%	Moderate	Strong For
	40% to 90%	Moderate	Strong For
	> 90%	Low	Conditional For
18+ years	< 40%	Moderate	Strong For
	40% to 90%	Moderate	Strong For
	> 90%	Low	Conditional For

CFF – Cystic fibrosis foundation; ppFEV$_1$ – Percent predicted forced expiratory volume in 1 second; N/A – Not applicable.

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 3 year in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

30. Cystic Fibrosis (CF), Homozygous for the F508del (Phe508del) Mutation in the Cystic Fibrosis Transmembrane Regulator (CFTR) Gene. Approve for 3 years in patients who meet the following criteria (A, B, and C):

24. The patient is homozygous for the F508del (Phe508del) mutation in the CFTR gene (meaning the patient has two copies of the F508del [Phe508del] mutation); AND

25. The patient is ≥ 2 years of age; AND

26. 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

Orkambi 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. 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.

24. 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.

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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250. Ren CL, Morgan RL, Oermann C, et al. Cystic fibrosis foundation pulmonary guidelines: Use of CFTR modulator therapy in patients with cystic fibrosis. *Ann Am Thorac Soc*. 2018;15(3):271-280

OTHER REFERENCES UTILIZED

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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

29. 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:

27. 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.

28. 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.

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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251. Orkambi® [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; July 2019.
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254. Ren CL, Morgan RL, Oermann C, et al. Cystic fibrosis foundation pulmonary guidelines: Use of CFTR modulator therapy in patients with cystic fibrosis. *Ann Am Thorac Soc*. 2018;15(3):271-280.

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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PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis – Symdeko® (tezacaftor/ivacaftor and ivacaftor tablets – Vertex)

REVIEW DATE: 03/25/2020

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*	

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

25. Cystic Fibrosis (CF). Approve Symdeko for 3 years in patients who meet the following criteria A, B, AND C:

D) The patient meets ONE of the following conditions (i or ii):

a. The 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, or 3849 + 10kbC → T; OR

b. The patient has two copies of the F508del mutation; AND

E) The patient is ≥ 6 years of age; AND

F) Symdeko is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of CF.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Symdeko 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. **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]

95. 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

266. Symdeko™ tablets [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; December 2019.
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Other References Utilized

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PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis – Trikafta™ (elexacaftor/tezacaftor/ivacaftor tablets; ivacaftor tablets, co-packaged – Vertex)

REVIEW DATE: 10/23/2019

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.[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.

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.

The F508del is the most common mutation found in patients with CF, in 2017 it was estimated that 25,276 patients with CF had at least one copy of the F508del mutation (85.8% of the CF population).[6]

Prevalence of F508del Mutations in Patients with CF in 2017.[6]

F508del Mutation	Percent of all Patients with CF
Homozygous F508del	45.3%
Heterozygous F508del	40.9%
Neither F508del or Unknown	13.7%

CF – Cystic fibrosis.

Clinical Efficacy

The efficacy of Trikafta in patients ≥ 12 years of age with CF was evaluated in two Phase III, double-blind, controlled trials.[1] Patients in both studies continued on their other standard-of-care CF therapies (e.g., bronchodilators, inhaled antibiotics, dornase alfa, and hypertonic saline).

Trial 1 was a 24-week, randomized, double-blind, placebo-controlled study in patients who had an F508del mutation on one allele and a mutation on the second allele either with no CFTR protein or a CFTR protein that is not responsive to Symdeko.[1] An interim analysis was planned when ≥ 140 patients completed Week 4 and ≥ 100 patients completed Week 12. Of the 403 patients included in the interim analysis, the treatment difference between Trikafta and placebo for the mean absolute change from baseline in percent predicted forced expiratory volume in 1 second (ppFEV1) at Week 4 was 13.8% (95% confidence interval [CI]: 12.1, 15.4; P < 0.0001). The treatment difference between Trikafta and placebo for mean absolute change in ppFEV1 from baseline through Week 24 was 14.3% (95% CI: 12.7, 15.8; P < 0.0001).

Trial 2 was a 4-week, randomized, double-blind, active-controlled study in patients who were homozygous for the F508del mutation (n = 107).[1] Patients received Symdeko every 12 hours during a 4-week, open-label, run-in period and were then randomized and dosed to receive Trikafta or Symdeko every 12 hours during a 4-week, double-blind, treatment period. The mean ppFEV1 at baseline, following the 4-week open-label run-in period with Symdeko was 60.9% (range: 35.0%, 89.0%). The primary endpoint was mean absolute change in ppFEV1 from baseline at Week 4 of the double-blind treatment period. Treatment with Trikafta compared to Symdeko resulted in a statistically significant improvement in ppFEV1 of 10.0% (95% CI: 7.4, 12.6; P < 0.0001).

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 the duration 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. All approvals are provided for 3 years unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

30. Cystic Fibrosis (CF). Approve for 3 years if the patient meets the following criteria (A, B, and C):
- **A)** The patient is ≥ 12 years of age; AND
- **B)** Trikafta is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of CF; AND
- **C)** The patient has at least one copy of the F508del mutation in the cystic fibrosis conductance regulator gene.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Trikafta 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. 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]

31. 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.

32. 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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118. Kalydeco™ tablets and oral granules [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; April 2019.
119. Orkambi™ tablets and oral granules [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; July 2019.
120. Symdeko™ tablets [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; June 2019.
121. Ren CL, Morgan RL, Oermann C, et al. Cystic Fibrosis Foundation Pulmonary Guidelines: Use of cystic fibrosis trasmembrane conductance regulator modulator therapy in patients with cystic fibrosis. *Ann Am Thorac Soc*. 2018;15(3):271-280.
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PRIOR AUTHORIZATION POLICY

POLICY: Nocdurna® (desmopressin acetate sublingual tablets [27.7 mcg and 55.3 mcg] – Ferring)

REVIEW DATE: 09/11/2019

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.

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 (SIADH) 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

In 2011 a consensus statement was published regarding the evaluation and treatment of nocturia.[2] Nocturnal polyuria is defined as nocturnal urine volume exceeding 20% of the total 24-hour urine volume in patients < 65 years of age and exceeding 33% of the total 24-hour urine volume in patients ≥ 65 years of age. Most patients initially respond to nocturia by engaging in one or more lifestyle modifications. The statement suggests that for patients whose nocturia is related to nocturnal polyuria, treatment that reduces nocturnal urine volumes may be appropriate. Due to the specific antidiuretic action of desmopressin, it is the pharmacological therapy of choice for patients with nocturia when nocturnal polyuria is present. Desmopressin appears well-tolerated with hyponatremia as the only potentially serious adverse event. Many patients diagnosed with benign prostatic hypertrophy (BPH) or overactive bladder (OAB) have comorbid nocturnal polyuria, which may be resistant to treatment with $alpha_1$ blockers and/or anticholinergics. Therefore, for patients with BPH or OAB and concomitant nocturnal polyuria, combined use of desmopressin should be considered.

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 Indication

31. 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)** The patient is ≥ 18 years of age; AND
- **H)** Nocdurna is prescribed by or in consultation with a urologist, a geriatrician, or an endocrinologist; AND
- **I)** 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
- **J)** The patient has tried non-pharmacologic techniques or lifestyle interventions to manage the nocturia (e.g., nighttime fluid restriction, avoidance of caffeine and alcohol, earlier timing of medications, leg elevation and/or use of compression stockings); AND
- **K)** Prior to desmopressin therapy, the patient awakens at least two times per night to void; AND
- **L)** The patient has serum sodium concentrations within the normal range (135 to 145 mmol/L); AND
- **M)** The prescribing physician 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 (SIADH) secretion.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Nocdurna 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.)

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

143. Nocdurna® sublingual tablets [prescribing information]. Parsippany, NJ: Ferring Pharmaceuticals; June 2018.

144. Weiss JP, Blaivas JG, Bliwise DL, et al. The evaluation and treatment of nocturia: a consensus statement. *BJU Int.* 2011;108:6-21.

PRIOR AUTHORIZATION POLICY

POLICY: Desmopressin Products – Noctiva™ (desmopressin acetate nasal spray for intranasal use [0.83 mcg/0.1 mL and 1.66 mcg/0.1 mL] – Avadel)

REVIEW DATE: 09/11/2019

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. Before initiating Noctiva it is recommended that the diagnosis of nocturnal polyuria has been confirmed with a 24-hour urine collection. It is recommended to check serum sodium concentrations prior to initiating or resuming Noctiva and throughout treatment. If hyponatremia occurs, Noctiva may need to be temporarily or permanently discontinued.

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 (SIADH) 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.

Other Desmopressin Therapies

Nocdura® (desmopressin acetate sublingual tablets) is a vasopressin analog indicated for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least two times per night to void.[2] The FDA-approved dose in women is 27.7 mcg daily (25 mcg desmopressin), 1 hour before bedtime, given sublingually without water. The recommended dose in men is 55.3 mcg daily (50 mcg desmopressin), 1 hour before bedtime, administered sublingually without water. The pharmacokinetics of Nocdurna have not been established; however, overall mean bioavailability was 0.25% with higher sublingual desmopressin doses.

Many other desmopressin products are available in various formulations (oral tablets, nasal spray, injection).[3-7] None of the agents are indicated for use in nocturia due to nocturnal polyuria.

- DDAVP® tablets (desmopressin acetate oral tablets, generic [0.1 mg and 0.2 mg]) are indicated for use in central diabetes insipidus and primary nocturnal enuresis.[4] Oral bioavailability is 0.16%.

- DDAVP injection (desmopressin acetate injection, generic [4 mcg/mL]) is indicated for the treatment of hemophilia A and von Willebrand's disease (type 1) [given by intravenous infusion], as well as for central (cranial) diabetes insipidus (administered subcutaneously or as a direct intravenous injection).[4]
- DDAVP nasal spray (desmopressin acetate nasal spray [10 mcg per 0.1 mL]) and DDAVP rhinal tubule (0.1 mg per 1 mL) are indicated for use in central cranial diabetes insipidus.[5,6] Stimate nasal spray (desmopressin acetate nasal spray [150 mcg per 0.1 mL]) is indicated for use in hemophilia A and von Willebrand's Disease (type 1).[6] Per Stimate product labeling, intranasal bioavailability is 3.3% to 4.1%.[7]

Noctiva delivers a much lower rate of desmopressin medication per spray (0.83 mcg or 1.66 mcg per spray) than either intranasal desmopressin product (approximately 10 times less than DDAVP nasal spray and around 100 times less than Stimate nasal spray).[1] However, 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]

Data with Oral Desmopressin in Nocturia

Many reviews and clinical studies have investigated the effect of oral desmopressin in patients with nocturia.[8-26] Desmopressin was superior to placebo in reducing the overall number of nocturnal voids.[9] A Cochrane review of desmopressin for treating nocturia in men (2017) concluded that desmopressin may reduce the frequency of urination at night in many men compared with placebo when treated for 3 to 12 months.[11] Other reviews also support the use of desmopressin in both tablet and orally disintegrating tablet formulations for patients with nocturia.[12-14] Other studies also detailed the use of oral desmopressin in the management of nocturia in various clinical scenarios.[15-26]

Guidelines

In 2011 a consensus statement was published regarding the evaluation and treatment of nocturia.[27] Nocturnal polyuria is defined as nocturnal urine volume exceeding 20% of the total 24-hour urine volume in patients < 65 years of age and exceeding 33% of the total 24-hour urine volume in patients ≥ 65 years of age. Most patients initially respond to nocturia by engaging in one or more lifestyle modifications. The statement suggests that for patients whose nocturia is related to nocturnal polyuria, treatment that reduces nocturnal urine volumes may be appropriate. Due to the specific antidiuretic action of desmopressin, it is the pharmacological therapy of choice for patients with nocturia when nocturnal polyuria is present. Desmopressin appears well-tolerated with hyponatremia as the only potentially serious adverse event. Many patients diagnosed with benign prostatic hypertrophy (BPH) or overactive bladder (OAB) have comorbid nocturnal polyuria, which may be resistant to treatment with alpha$_1$ blockers and/or anticholinergics. Therefore, for patients with BPH or OAB and concomitant nocturnal polyuria, combined use of desmopressin should be considered.

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 Indication

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)** The patient is ≥ 50 years of age; AND
   - **B)** Noctiva is prescribed by or in consultation with a urologist, a geriatrician, or an endocrinologist; AND
   - **C)** 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
   - **D)** The patient has tried non-pharmacologic techniques or lifestyle interventions to manage the nocturia (e.g., nighttime fluid restriction, avoidance of caffeine and alcohol, earlier timing of medications, leg elevation and/or use of compression stockings); AND
   - **E)** Prior to desmopressin therapy, the patient awakens at least two times per night to void; AND
   - **F)** The patient has serum sodium concentrations within the normal range (135 to 145 mmol/L); AND
   - **G)** The patient tried one of Nocdurna (desmopressin acetate sublingual tablets) or oral desmopressin acetate tablets (DDAVP tablets, generics); AND
   - **H)** The prescribing physician 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 (NYHA) class II to IV congestive heart failure (CHF); OR
     - **v.** Polydipsia; OR
     - **vi.** Known or suspected syndrome of inappropriate antidiuretic hormone (SIADH) secretion.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Noctiva 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.)

97. 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. Use of Noctiva has not been studied in pediatric patients. Desmopressin tablets (DDAVP tablets) are indicated for the management of primary nocturnal enuresis in pediatric patients.[3]

98. 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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146. Nocdurna® sublingual tablets [prescribing information]. Parsippany, NJ: Ferring Pharmaceuticals; June 2018.
147. DDAVP® tablets [prescribing information]. Parsipanny, NJ: Ferring Pharmaceuticals; December 2014.
148. DDAVP® injection [prescribing information]. Parsipanny, NJ: Ferring Pharmaceuticals; April 2015.
149. DDAVP® nasal spray [prescribing information]. Parsipanny, NJ: Ferring Pharmaceuticals; April 2015.
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PRIOR AUTHORIZATION POLICY

POLICY: Diabetes – Glucagon-Like Peptide-1 Agonists

- 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: 10/09/2019

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.[2] Victoza is also indicated to reduce the risk of major adverse cardiovascular (CV) events (MACE) [CV death, non-fatal myocardial infarction [MI], or non-fatal stroke) in adults with type 2 diabetes mellitus and established CV disease.

Guidelines/Consensus or Position Statements

The American Diabetes Association (ADA) Standards of Care (2019), American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE), and the European Association for the Study of Diabetes (EASD) generally make similar recommendations for the management of hyperglycemia in patients with type 2 diabetes.[10-12] In general, metformin is the first-line medication, additional treatment is guided by adverse event profiles, glycemic efficacy, and other patient factors.

According to the ADA Standards of Care (2019), among patients with type 2 diabetes with established atherosclerotic CV disease (ASCVD), sodium-glucose co-transporter 2 (SGLT-2) inhibitors or GLP-1 agonists with demonstrated CV disease benefit (Victoza > Ozempic > Bydureon) 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 dual or triple antihyperglycemic therapy; GLP-1 agonists should be initiated before insulin in most patients with type 2 diabetes. Of note, these guidelines have not yet been updated to address CV outcomes data for Trulicity or Rybelsus.

Guidelines from the European Society of Cardiology and the EASD on diabetes, pre-diabetes, and CV diseases (2019) state that patients with type 2 diabetes and ASCVD or high CV risk should be initiated on an SGLT-2 inhibitor or GLP-1 receptor agonist, regardless of whether the patient is already on metformin.[11] The guidelines go on to say that for patients with prevalent CVD, Victoza or Jardiance® (empagliflozin tablets) should be recommended to reduce risk for mortality. It is noted that the benefits of GLP-1 agonists are most likely derived through reduction in arteriosclerosis-related events, whereas SGLT-2 inhibitors seem to reduce HF-related endpoints. For patients without ASCVD/high CV risk, metformin is the first-line recommendation for monotherapy.

AACE recommendations (2019) include a glycemic control algorithm based on glycosylated hemoglobin (HbA_{1C}) at entry.[12] For those with an $HbA_{1C} < 7.5\%$, but not at target ($\leq 6.5\%$ per the AACE guidelines), monotherapy is recommended. Metformin is generally the preferred agent, but a GLP-1 agonist or SGLT-

2 inhibitor with proven CVD/CKD benefit is recommended for patients in whom those comorbidities are present. For patients with higher HbA_{1C} at treatment initiation or who fail to reach their glycemic target on metformin monotherapy, combination therapy is recommended with metformin plus other agents; the strength of recommendation is greatest for GLP-1 agonists or SGLT-2 inhibitors.

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

FDA-Approved Indications

Coverage is recommended in those who meet the following criteria:

1. **Type 2 Diabetes Mellitus.** Approve for 3 years.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

The GLP-1 agonists in this policy 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.)

33. **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]

34. **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.

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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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.

99. 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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PRIOR AUTHORIZATION POLICY

POLICY: Dronabinol

- Marinol® (dronabinol capsules – AbbVie, generics)
- Syndros® (dronabinol oral solution – Insys)

REVIEW DATE: 10/23/2019

OVERVIEW

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 (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. 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.

The National Comprehensive Cancer Network (NCCN) guidelines regarding the treatment of emesis (version 1.2019) include various regimens depending upon the emetogenic potential of the chemotherapy agent(s) being administered.[3] 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, dexamethasone, and nabilone (discontinued in US). The agent should be from a different drug class to the current regimen, but no preference is given.

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.[4] Published studies supporting these off-label uses are lacking.

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 due to the potential for off-label use 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

26. 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 prescribing physician, 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 (e.g., 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); AND
- **B)** The 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 prescribing physician, 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) The patient has tried generic dronabinol capsules; OR
   B) The 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) The patient has failed to respond adequately to at least two conventional antiemetic treatments (e.g., 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); AND
   B) The patient meets ONE of the following (i or ii):
      i. The patient has tried generic dronabinol capsules; OR
      ii. The patient cannot swallow or has difficulty swallowing capsules.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Dronabinol 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.)

100. **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.

101. **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.

102. **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.

103. 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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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

32. 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 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.

iv. Patient has a history of at least one 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) Patient is Currently Receiving Enspryng. 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 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.

iv. 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:

36. 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.

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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PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Adagen® (pegademase bovine injection for intramuscular use – Leadiant [obsolete 6/30/2019])

REVIEW DATE: 11/20/2019

OVERVIEW

Adagen is a modified enzyme used for enzyme replacement therapy for the treatment of severe combined immunodeficiency disease (SCID) 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.

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

A consensus statement for management of ADA-SCID was recently updated (2018).[4] 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. This should be followed by genetic testing to confirm bi-allelic mutations in the *ADA* gene. 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. 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. All approvals are provided for 1 year.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Adagen is recommended for those who meet the following criteria.

FDA-Approved Indications

3. Adenosine Deaminase Severe Combined Immunodeficiency (ADA-SCID). Approve Adagen for 1 year in patients meeting both of the following criteria (A and B):

A) The 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. The 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

Adagen 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. 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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17. Hershfield M. GeneReviews [Internet]. Updated March 16, 2017. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1483/. Accessed on November 14, 2019.
18. Gaspar HB, Aiuti A, Porta F, et al. How I treat ADA deficiency. *Blood*. 2009;114:3524-3532. Available at: http://www.bloodjournal.org/content/114/17/3524?sso-checked=true. Accessed on November 14, 2019.

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PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Aldurazyme® (laronidase solution for intravenous infusion – Genzyme Corporation)

REVIEW DATE: 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

31. 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.

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

130. Aldurazyme® solution for intravenous infusion [prescribing information]. Novato, CA: BioMarin Pharmaceutical Inc.; December 2019.
131. Muenzer J, Wraith JE, Clarke LA, et al. Mucopolysaccharidosis I: Management and treatment guidelines. *Pediatrics*. 2009;123:19-29.
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134. Martins AM, Dualibi AP, Norato D, et al. Guidelines for the management of mucopolysaccharidosis type I. *J Pediatr*. 2009;155(Suppl 2):S32-S46.

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Elaprase® (idursulfase injection for intravenous use – Shire Human Genetic Therapies)

REVIEW DATE: 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

32. 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.

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

135. Elaprase® injection for intravenous use [prescribing information]. Lexington, MA: Shire Human Genetic Therapies, Inc.; November, 2018.

136. 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.
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139. 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.

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

33. 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.

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

140. Fabrazyme® injection [prescribing information]. Cambridge, MA: Genzyme Corporation; December 2018.
141. Schiffmann R. Fabry Disease. *Handb Clin Neurol*. 2015;132:231-248.
142. 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.
143. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Kanuma™ (sebelipase alfa injection for intravenous use – Alexion Pharmaceuticals)

REVIEW DATE: 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

34. 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.

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

144. Kanuma™ injection [prescribing information]. Cheshire, CT: Alexion Pharmaceuticals; December 2015.
145. 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.
146. Erwin AL. The role of sebelipase alfa in the treatment of lysosomal acid lipase deficiency. *Ther Adv Gastroenterol*. 2017;10:553-562.

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

35. 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.

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

147. Lumizyme® injection [prescribing information]. Cambridge, MA: Genzyme Corporation; February 2020.

148. Chien YH, Hwu WL, Lee NC. Pompe disease: Early diagnosis and early treatment make a difference. *Pediatr Neonatol*. 2013;54:219-227.
149. 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.
150. Cupler EJ, Berger KI, Leshner RT, et al. Consensus treatment recommendations for late-onset Pompe disease. *Muscle Nerve*. 2012;45:319-333.

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

36. 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.

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

151. Mepsevii injection [prescribing information]. Novato, CA: Ultragenyx Pharmaceutical; December 2019.
152. Montano AM, Lock-Hock N, Steiner RD, et al. Clinical course of sly syndrome (mucopolysaccharidosis type VII). *J Med Genet*. 2016;53:403-418.
153. 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.

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

37. 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.

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

154. Naglazyme® injection for intravenous use [prescribing information]. Novato, CA: BioMarin Pharmaceutical, Inc.; December 2019.
155. Harmatz PR, Shediac R. Mucopolysaccharidosis VI: Pathophysiology, diagnosis and treatment. *Front Biosci*. 2017;22:385-406.
156. Vairo F, Federhen A, Baldo G, et al. Diagnostic and treatment strategies in mucopolysaccharidosis VI. *Appl Clin Genet*. 2015;8:245-255.

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Revcovi® (elapegademase-lvlr injection for intramuscular use – Leadiant)

DATE REVIEWED: 11/20/2019

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]

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

A consensus statement for management of ADA-SCID was recently updated (2018).[4] 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. 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. 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. All approvals are provided for 1 year.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Revcovi is recommended for those who meet the following criteria.

FDA-Approved Indications

4. **Adenosine Deaminase Severe Combined Immunodeficiency (ADA-SCID).** Approve Revcovi for 1 year in patients meeting both of the following criteria (A and B):
   - **A)** The 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.** The 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

Revcovi 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. 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. Revcovi® [prescribing information]. Gaithersburg, MD: Leadiant Biosciences, Inc; October 2018.
21. Hershfield M. GeneReviews [Internet]. Updated March 16, 2017. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1483/. Accessed on November 14, 2019.
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23. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Enzyme Replacement Therapy – Strensiq® (asfotase alfa for subcutaneous use – Alexion Pharmaceuticals, Inc.)

REVIEW DATE: 07/17/2019

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

33. Hypophosphatasia – Perinatal/Infantile- and Juvenile-Onset. Approve for 3 years if the patient meets ALL of the following criteria (A, B, C, AND D):

27. 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

28. 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

29. Disease onset ≤ 18 years of age; AND

30. 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.

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
182. Strensiq® injection [prescribing information]. Cheshire, CT: Alexion Pharmaceuticals, Inc.; January, 2018.
183. White MP. Hypophosphatasia: Enzyme Replacement Therapy Brings New Opportunities and New Challenges. *J Bone Miner Res*. 2017;32:667-675.
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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.

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

38. 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.

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
157. Sucraid® oral solution [prescribing information]. Vero Beach, FL: QOL Medical; February 2019.
158. 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.
159. Cohen SA. The clinical consequences of sucrose-isomaltase deficiency. *Mol Cell Pediatr*. 2016;3:5.
160. 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.

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

39. 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.

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

161. Vimizim® injection for intravenous use [prescribing information]. Novato, CA: BioMarin Pharmaceuticals; December 2019.
162. 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.
163. Tomatsu S, Yasuda E, Patel P, et al. Morquio A syndrome: Diagnosis and current and future therapies. *Pediatr Endocrinol Rev*. 2014;12:141-151.
164. Regier DS, Tanpaiboon P. Role of elosulfase alfa in mucopolysaccharidosis IVA. *Appl Clin Genet*. 2016;9:67-74.

PRIOR AUTHORIZATION POLICY

POLICY: Erectile Dysfunction – Alprostadil for injection
- Caverject® (alprostadil for injection – Pharmacia & Upjohn [Pfizer])
- Caverject Impulse® (alprostadil for injection – Pharmacia & Upjohn [Pfizer])
- Edex® (alprostadil for injection – Endo Pharmaceuticals, Inc.)
- MUSE® (alprostadil urethral suppository – MEDA Pharmaceuticals)

REVIEW DATE: 8/28/2019

OVERVIEW

Alprostadil belongs to the family of prostaglandins (specifically prostaglandin E_1 [PGE_1]), which are naturally occurring lipids with various pharmacological effects, including vasodilation and inhibition of platelet aggregation.[1-4] They are naturally present in the seminal vesicles and cavernous tissue of males.[5] As a smooth muscle relaxant, alprostadil has demonstrated efficacy for the treatment of erectile dysfunction (ED). It binds to specific receptors in the human penile tissue, and induces erection by relaxation of trabecular smooth muscle and by dilation of cavernous arteries.[3] This leads to an expansion of the lacunar spaces and entrapment of blood by compressing the venules, a process referred to as the corporal veno-occlusive mechanism.

The available injectable alprostadil products are: Caverject, Caverject Impulse (disposable, single-dose, dual chamber syringe system), and Edex. MUSE is a single-use, medicated transurethral system for the delivery of alprostadil directly in the urethra.[4] It is suspended in polyethylene glycol and is formed into a medicated pellet. 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]

Other Uses with Supportive Evidence

Prophylaxis after Radical Prostatectomy

The treatments most studied for penile rehabilitation are alprostadil (injections or intraurethral suppository) and oral phosphodiesterase type 5 (PDE5) inhibitors.[6] 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.[7-13]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of alprostadil injections and suppository administered via intracavernous or intraurethral routes, respectively. Intravenous (IV) or other routes of administration of alprostadil is not covered by this policy. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of alprostadil injections (e.g., Edex, Caverject) and suppository (e.g., MUSE) is recommended in those who meet the following criteria:

FDA-Approved Indications

34. Erectile Dysfunction (ED). Approve for 1 year.

Other Uses with Supportive Evidence

35. 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)** Alprostadil (e.g., Edex, Caverject, MUSE) is prescribed by or in consultation with an urologist

36. 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

Alprostadil products (Caverject, Caverject Impulse, Edex, MUSE) 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.

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

270. Caverject® [prescribing information]. New York, NY: Pharmacia and Upjohn Company (Pfizer); December 2017.
271. Caverject Impulse® [prescribing information]. New York, NY: Pharmacia and Upjohn Company (Pfizer); October 2016.
272. Edex® [prescribing information]. Malvern, PA: Endo Pharmaceuticals, Inc.; July 2018.
273. MUSE [prescribing information]. Somerset, NJ: Meda Pharmaceuticals; April 2018.
274. Clinical Pharmacology [database online]. Tampla, FL: Gold Standard, Inc.; 2019. Available at http://www.clinicalpharmacology-ip.com/default.aspx. Accessed August 23, 2019. Search term: Caverject.
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281. 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.
282. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Erectile Dysfunction – Viagra® (sildenafil tablets – Pfizer; generics)

REVIEW DATE: 8/28/2019

OVERVIEW

Sildenafil (Viagra, generics) are a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5).[1] It enhances the effect of nitric oxide by inhibiting PDE5, which is responsible for degradation of cGMP in the corpus cavernosum of the penis. When sexual stimulation causes local release of nitric oxide, inhibition of PDE5 by Viagra (sildenafil) cause increased levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum. Sildenafil (Viagra, generics) are indicated for the treatment of erectile dysfunction (ED).

Other Uses with Supportive Evidence

Pulmonary arterial hypertension

Sildenafil tablets (Revatio®) are approved for pulmonary arterial hypertension. Revatio contains the same active ingredient as Viagra, sildenafil citrate.[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 PAH based on case reports and placebo-controlled, double-blind studies.[3-14] Doses of Viagra that were used in these reports ranged from 25 mg twice daily (BID) to 100 mg five times daily. Patients will have usually been started on Revatio 20 mg three times daily (TID).

Raynaud phenomenon

Case studies show Viagra has additionally been effective in patients with Raynaud phenomenon (usually with scleroderma) who have digital ischemia, gangrene, or ulcers.[15-18] In a double-blind, placebo-controlled, crossover study, 16 patients with symptomatic secondary Raynaud disease resistant to vasodilatory therapy received 50 mg of Viagra BID or placebo for 4 weeks.[19] While on Viagra, the mean frequency of Raynaud attacks was significantly lower, the cumulative attack duration was significantly shorter, and the mean Raynaud's Condition Score was significantly lower. Capillary blood flow velocity increased in every patient and the mean capillary flow velocity increased by > 400% in all patients after therapy with Viagra.

Benign prostatic hyperplasia (BPH)

Sildenafil (Viagra, generics) have been shown to be effective in BPH. A meta-analysis of several randomized controlled trials comparing PDE5 inhibitors vs. placebo or α_1-blockers, and PDE5 inhibitors in combination therapy with α_1-blockers was conducted.[20] A total of 12 studies were included in the analysis and the median follow-up for all trials was 12 weeks. The analysis of these trials showed that the use of PDE5 inhibitors alone was associated with a significant improvement of the IIEF score (+5.5; $P < 0.0001$) and IPSS (-2.8; $P < 0.0001$), but not in the maximum urinary flow rate (Q_{max}) compared with placebo. There were also statistically significant improvements in the IIEF score, IPSS score and Q_{max} for the combination of PDE5 inhibitors and α_1-blockers as compared with α_1-blockers alone.

The European Association of Urology (EAU) guidelines note that PDE5 inhibitors can be used in men with moderate-to-severe LUTS with or without ED.[21] The guidelines add that based on the results from a meta-analysis[20], younger men with lower body mass index and more severe LUTS benefit the most from PDE5 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.[22-24]

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. Results of many clinical trials regarding the effectiveness of PDE5 inhibitors on post radical prostatectomy ED make them the gold standard of treatment.[25]

High-Altitude Pulmonary Edema
Published guidelines for the prevention of HAPE recommend nifedipine as the preferred pharmacologic treatment option in patients who have a history of HAPE.[26] Other pharmacologic therapies mentioned in the guidelines for the prevention and/or treatment of HAPE include salmeterol, Cialis, Viagra, dexamethasone, or acetazolamide. For Viagra, published guidelines recommend a dose of 50 mg every 8 hours for the prevention of HAPE.

POLICY STATEMENT
Prior authorization is recommended for prescription benefit coverage of sildenafil (Viagra, generic). All approvals are provided for the duration noted below.

Automation: When available, the ICD-9/ICD-10 codes for impotence of organic origin (ICD-9: 607.84) or 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; PDE5 inhibitor approval for use in women is always determined by prior authorization criteria.

Note: PDE5 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 PDE5 inhibitor.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of sildenafil (Viagra, generics) are recommended in those who meet one of the following criteria:

FDA-Approved Indications

27. **Erectile Dysfunction (ED)**. Approve for 1 year.

Other Uses with Supportive Evidence

28. **Pulmonary Arterial Hypertension (PAH)**. Approve for 1 year.

29. **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 (e.g., amlodipine, felodipine, nifedipine), α-adrenergic blockers (e.g., prazosin), nitroglycerin, losartan, fluoxetine, or angiotensin converting enzyme (ACE) inhibitors; OR

B) Patient has tried one vasodilator (e.g., Flolan® [epoprostenol for injection], Edex® [alprostadil for injection], Tracleer® [bosentan tablets]).

30. Benign Prostatic Hyperplasia (BPH). Approve for 1 year if the patient meets one of the following criteria (A or B):
A) Patient has tried an α_1-blocker (e.g., Cardura® XL [doxazosin extended-release tablets], terazosin tablets/capsules, tamsulosin capsules, alfuzosin extended-release tablets); OR
B) Patient has tried a 5α-reductase inhibitor (e.g., finasteride tablets, dutasteride capsules).

Note: For men with ED/BPH, 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) Sildenafil (Viagra, generics) are 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 (i.e., nifedipine, Serevent® [salmeterol inhalation powder], dexamethasone, acetazolamide, Cialis® [tadalafil tablets]) for the treatment or prevention of HAPE.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Sildenafil (Viagra, 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. (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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PRIOR AUTHORIZATION POLICY

POLICY: Erectile Dysfunction – Stendra™ (avanafil tablets – Mist Pharmaceuticals, LLC)

REVIEW DATE: 08/28/20019

OVERVIEW

Stendra is a phosphodiesterase type 5 (PDE5) inhibitor indicated for the treatment of erectile dysfunction (ED).[1] Stendra and the other PDE5 inhibitors have the same mechanism of action in ED; they enhance the effect of nitric oxide by inhibiting PDE5, which degrades cyclic guanosine monophosphate (cGMP). cGMP is responsible for producing smooth muscle relaxation in the corpus cavernosum of the penis, which results in increased blood flow and erection. Sexual stimulation is required for all PDE5 inhibitors to be effective since it initiates the local release of nitric oxide. Though all PDE5 inhibitors have the same mechanism of action, they still differ with regards to some pharmacokinetic parameters. For example, compared with the other agents, Stendra has a faster onset of action and can be taken as early as ~15 minutes before sexual activity.

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-9/ICD-10 codes for impotence of organic origin (ICD-9: 607.84) or 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; PDE5 inhibitor approval for use in women is always determined by prior authorization criteria.

Note: PDE5 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 PDE5 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 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. **Benign Prostatic Hyperplasia (BPH).** There are no data available with the use of Stendra for BPH.

107. **Prophylaxis of Erectile Dysfunction (ED) after Radical Prostatectomy.** The efficacy of Stendra for the treatment of ED after nerve-sparing radical prostatectomy has been demonstrated in a Phase III study.[2] There are no data available for the prophylactic use (early penile rehabilitation) of Stendra in this patient population.

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
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PRIOR AUTHORIZATION POLICY

POLICY: Erectile Dysfunction – Cialis® (tadalafil tablets – Eli Lilly; generics)

REVIEW DATE: 08/28/2019

OVERVIEW

Tadalafil (Cialis, generics), selective inhibitors of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5), are indicated for the treatment of erectile dysfunction (ED), the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH), and for the treatment of ED and the signs and symptoms of BPH (ED/BPH).[1] If Cialis (tadalafil) is used with finasteride to initiate BPH treatment, such use is recommended for up to 26 weeks. This is because the incremental benefit of Cialis (tadalafil) decreases from 4 weeks to 26 weeks, and the benefit beyond 26 weeks is unknown.

Other Uses with Supportive Evidence

Limited information is available with the use of Cialis in Raynaud disease[2-4] and prophylaxis after radical prostatectomy.[5-7]

Pulmonary arterial hypertension (PAH)

Adcirca (or generics of Adcirca) contain the same active ingredient as tadalafil (Cialis, generics) and are indicated for the treatment of PAH.[8] Tadalafil (Cialis, generics) are available in 2.5 mg, 5 mg, 10 mg, and 20 mg tablets. Adcirca (or generics of Adcirca) is available as 20 mg tablets. The approved dose of Adcirca for PAH is 40 mg QD with dosage adjustments recommended for patients with renal impairment, hepatic impairment, and in those using ritonavir. Tadalafil (Cialis, generics) has been used for PAH based on case reports and placebo-controlled, double-blind studies.[8-10]

High-Altitude Pulmonary Edema

Published guidelines for the prevention of HAPE recommend nifedipine as the preferred pharmacologic treatment option in patients who have a history of HAPE.[11] Other pharmacologic therapies mentioned in the guidelines for the prevention and/or treatment of HAPE include salmeterol, Cialis, Viagra, dexamethasone, or acetazolamide. For Viagra, published guidelines recommend a dose of 50 mg every 8 hours for the prevention of HAPE. A recent review article on acute high-altitude sickness notes that nifedipine 30 mg BID in a slow-release formulation, Cialis 10 mg BID, and dexamethasone 8 mg BID appear to be similarly effective in lowering pulmonary artery pressure and reducing the incidence of HAPE from approximately 70% to ≤ 10%.[12]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of tadalafil (Cialis, generics). All approvals are provided for the duration noted below.

Automation: When available, the ICD-9/ICD-10 codes for impotence of organic origin (ICD-9: 607.84) or 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; PDE5 inhibitor approval for use in women is always determined by prior authorization criteria.

Note: PDE5 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 PDE5 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 (ED)**. Approve for 1 year.

9. **Benign Prostatic Hyperplasia (BPH).** Approve for 1 year if the patient meets ONE of the following criteria (A or B):
   A) Patient has tried an α_1-blocker (e.g., Cardura® XL [doxazosin extended-release tablets], terazosin tablets/capsules, tamsulosin capsules, alfuzosin extended-release tablets); OR
   B) Patient has tried a 5α-reductase inhibitor (e.g., finasteride, dutasteride).

   Note: For men with ED/BPH, 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: calcium channel blockers (e.g., amlodipine, felodipine, nifedipine), α-adrenergic blockers (e.g., prazosin), nitroglycerin, losartan, fluoxetine, or angiotensin converting enzyme (ACE) inhibitors; OR
    B) Patient has tried one vasodilator (e.g., 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) Tadalafil (Cialis, generics) are 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). 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 (i.e., nifedipine, Serevent® [salmeterol inhalation powder], dexamethasone, acetazolamide, Viagra® [sildenafil tablets]) for treatment or prevention of HAPE.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Tadalafil (Cialis, generics) 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.

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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OTHER REFERENCES UTILIZED

- Goundry B, Bell L, Langtree M, et al. Diagnosis and management of Raynaud's phenomenon. *BMJ.* 2012;344:e289.

PRIOR AUTHORIZATION POLICY

POLICY: Erectile Dysfunction

- Levitra® (vardenafil tablets – GlaxoSmithKline; generics)
- Staxyn™ (vardenafil orally disintegrating tablet – GlaxoSmithKline; generics)

REVIEW DATE: 08/28/2019

OVERVIEW

Vardenafil (Levitra, generics) and vardenafil orally disintegrating tablets (ODT) [Staxyn, generics] are selective inhibitors of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). They are indicated for the treatment of erectile dysfunction (ED).[1] Vardenafil (Levitra, generics) are available as a 2.5 mg, 5 mg, 10 mg, and 20 mg film-coated tablet and vardenafil ODT (Staxyn, generics) are available as a 10 mg ODT.[1-2] Because the ODT provides a higher systemic exposure than the film-coated tablet, the 10 mg ODT and film-coated tablets are not interchangeable.

Other Uses with Supportive Evidence

Raynaud phenomenon

Levitra (vardenafil) has been studied in patients with Raynaud phenomenon. In an open-label study in 40 patients with Raynaud disease (33 patients with secondary and 7 patients with primary Raynaud disease),

patients received Levitra 10 mg twice daily (BID) for 2 weeks.[3] Levitra improved digital blood flow in 28 patients and 12 patients did not respond. Twenty-four of the 40 patients reported a reduction of the total daily duration of Raynaud disease-related attacks, and the number and severity of attacks were reduced in 50% and 53% of patients, respectively. The Raynaud condition score (RCS) declined from a mean of 5.05 ± 0.38 to 3.54 ± 0.31 ($P < 0.001$). A double-blind, single-center, randomized, placebo-controlled, two-period, crossover study was conducted for 6 weeks using Levitra (10 mg BID) in patients (n = 53) with primary and secondary Raynaud Phenomenon.[4] The RCS and digital blood flow were assessed as primary endpoints. Levitra significantly reduced RCS on average by -0.45 compared with placebo ($P = 0.03$). Compared with placebo, Levitra also decreased the number (-0.51 vs. placebo; $P = 0.005$) and cumulative duration of Raynaud attacks per day (-11.43 minutes vs. placebo; $P = 0.003$). There was also a non-significant improvement in the digital blood flow.

Benign prostatic hyperplasia (BPH)

Levitra (vardenafil) was additionally studied in BPH. In a Phase IIb, multicenter, parallel-group, double-blind trial, 222 men with lower urinary tract symptoms (LUTS) secondary to BPH with or without concomitant ED were randomized to Levitra 10 mg or placebo BID for 8 weeks.[5] Patients had an International Prostate Symptom Score (IPSS) ≥ 12 (mean baseline score: 16.8). The primary efficacy parameters were the IPSS total score and the maximum urinary flow rate (Qmax) with 2.2 points difference in IPSS and 2 mL/sec in Qmax being significant. After 8 weeks there was a significant improvement in the IPSS total score for Levitra vs. placebo (-5.9 and -3.6, respectively; difference = 2.3; $P = 0.0013$). This improvement is comparable to those reported with α-blockers. Qmax did not change significantly with therapy, but baseline values were already close to normal. Levitra therapy was associated with a nominally statistically significant improvement in erectile function (EF) compared to placebo. A Phase III placebo-controlled study evaluated the efficacy of tamsulosin vs. tamsulosin plus Levitra in men with LUTS/BPH.[6] Patients (n = 60) were randomized to a 12-week treatment with Levitra 10 mg/day plus tamsulosin 0.4 mg/day or placebo and tamsulosin 0.4 mg/day. The primary endpoint was change from baseline to Week 2 and Week 12 of total IPSS score. Other subscores, including IPSS-bother score (IPSS-B), overactive bladder short-form questionnaire (OAB-q), and International Index of Erectile Function (IIEF) domain 5 scores were also considered. Both at Week 2 and Week 12, treatment with tamsulosin plus Levitra resulted in a significant change in IPSS, IPSS-B, and OAB-q scores. After 12 weeks of Levitra, a significant increase in Qmax and average urinary flow rate (Qave) was also noted.

Prophylaxis after radical prostatectomy

Levitra was studied in men following bilateral nerve-sparing radical prostatectomy in the largest study to date.[7] In this double-blind, double-dummy, multicenter, parallel-group study, 628 men were randomized to placebo, nightly Levitra 10 mg, or on-demand Levitra (flexible dose starting with 10 mg and titrated to either 5 mg or 20 mg) for 9 months starting within 14 days after undergoing a bilateral nerve-sparing radical prostatectomy. Patients had normal preoperative erectile function with an IIEF-erectile function (EF) domain (IIEF-EF) score ≥ 26 at screening without the use of therapy or devices for improvement of erections. After the 9-month treatment period patients entered a 2-month single-blind placebo washout period where the dose of Levitra could be titrated by the investigator to preserve subject blinding. In the open-label period Levitra 10 mg (titrated to either 5 or 20 mg) on-demand was used. The primary efficacy variable was the percentage of patients with an IIEF-EF score ≥ 22 (mild ED) after the 2-month washout period using last observation carried forward (LOCF) analysis. In all, 423 patients finished the study. The primary efficacy variable was not met. There was no statistically significant difference between the treatment groups in the percentage of patients with IIEF-EF score ≥ 22 at the end of washout; IIEF-EF scores ≥ 22 were attained in 28.9%, 24.1%, and 29.1% for placebo, Levitra nightly, and Levitra on-demand, respectively. At the end of the double-blind treatment period, the percentage of patients with IIEF-EF score ≥ 22 was statistically significantly better for Levitra on-demand vs. placebo ($P < 0.0001$): 24.8% (placebo),

32.0% (Levitra nightly), and 48.2% (Levitra on-demand). The efficacy of Levitra on-demand during the open-label phase was similar in all three study groups (i.e., regardless of the previous treatment).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Vardenafil tablets (Levitra, generics) and vardenafil ODT (Staxyn, generics). All approvals are provided for the duration noted below.

Automation: When available, the ICD-9/ICD-10 codes for impotence of organic origin (ICD-9: 607.84) or 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; PDE5 inhibitor approval for use in women is always determined by prior authorization criteria.

Note: PDE5 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 PDE5 inhibitor.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vardenafil tablets (Levitra, generics) or vardenafil ODT (Staxyn, generics) is recommended in those who meet one of the following criteria:

FDA-Approved Indications

11. Erectile Dysfunction (ED). 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 (e.g., amlodipine, felodipine, nifedipine), α-adrenergic blockers (e.g., prazosin), nitroglycerin, losartan fluoxetine, or angiotensin converting enzyme (ACE) inhibitors; OR
- **B)** Patient has tried one vasodilator (e.g., Flolan® [epoprostenol for injection], Edex® [alprostadil for injection], Tracleer® [bosentan tablets]).

3. Benign Prostatic Hyperplasia (BPH). Approve for 1 year if the patient meets one of the following criteria (A or B):
- **A)** Patient has tried an α_1-blocker (e.g., Cardura® XL [doxazosin extended-release tablets], terazosin tablets/capsules, tamsulosin capsules, alfuzosin extended-release tablets); OR
- **B)** Patient has tried a 5α-reductase inhibitor (e.g., finasteride tablets, dutasteride capsules).

Note: For men with ED/BPH, 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) Vardenafil (Levitra, generics) or vardenafil ODT (Staxyn, generics) is prescribed by or in consultation with an urologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Vardenafil (Levitra, generics) or vardenafil ODT (Staxyn, generics) 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. **Pulmonary Arterial Hypertension (PAH)**. In a 1-year, open-label, multicenter study conducted in China, 45 patients with PAH who were able to walk a maximum of 550 meters in a 6-minute walk test (no minimum) received Levitra.[8] At baseline 12% of patients were in World Health Organization (WHO) functional class IV; 64% of patients were in class III, and 24% of patients were in class II. Patients received Levitra 5 mg daily for one month and then 5 mg BID if no significant adverse effects occurred. Patients were reassessed at 3, 9 and 18 months. Mean baseline 6-minute walk distance (6MWD) was 409 ± 103 meters. The mean 6MWD increased by 70.7 ± 78.4 meters at 3 months ($P < 0.0001$) and 83.4 ± 91.8 meters at 14 ± 3 months. After 3 months, WHO functional class improved ($P < 0.0001$) and further improvement was noted at 14 ± 3 months ($P < 0.0001$ compared with baseline). At the end of the study, 11% of patients were in WHO class I, 69% of patients were in class II, 18% of patients were in class III, and 2% of patients were in class IV.

   In a double-blind, placebo-controlled study, patients (n = 66) in China with PAH were randomized 2:1 to receive Levitra 5 mg QD for 4 weeks, followed by 5 mg BID or placebo for 12 weeks.[9] After completing this phase, patients were treated with open-label Levitra (5 mg BID) for an additional 12 weeks. At Week 12, the mean placebo-corrected 6MWD was increased with Levitra by 69 meters (95% confidence interval [CI]: 41m, 91m; $P < 0.001$). This improvement was maintained in the extension-phase for a total of at least 24 weeks. There were also improvements in the mean placebo-corrected cardiac index, pulmonary arterial pressure and pulmonary vascular resistance (PVR) at Week 12. Larger, longer-term, randomized trials are needed to determine the safety and efficacy of Levitra in PAH. Revatio® (sildenafil tablets) and Adcirca® (tadalafil tablets) are indicated for the treatment of PAH.

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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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.

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.
8. 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.
9. 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.
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.

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

11. Mircera® solution for injection [prescribing information]. Basking Ridge, NJ: Vifor Pharma; August 2019.
12. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Fabry Disease – Galafold (migalastat capsules – Amicus Therapeutics, Inc.)

REVIEW DATE: 10/02/2019

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 whether 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

37. Fabry Disease. Approve for 3 years if the patient meets the following criteria (A, B, and C):
- ~~**31.**~~ The patient is 18 years of age or older; AND
- ~~**32.**~~ Has an amenable galactosidase alpha gene (GLA) variant based on *in vitro* assay data; AND
- **33.** Galafold 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

Galafold 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.)

109. 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 have not been established.[8] Galafold is not FDA approved for concurrent use with Fabrazyme.

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

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193. Warnock DG, Bichet DG, Holida M, et al. Oral Migalastat HCl Leads to Greater Systemic Exposure and Tissue Levels of Active α-Galactosidase A in Fabry Patients when Co-Administered with Infused Agalsidase. *PLoS ONE*. 2015;10: e0134341. doi:10.1371/journal.pone.0134341.

STEP THERAPY POLICY

POLICY: Fenofibrate Step Therapy Policy

- Antara® (fenofibrate capsules – Lupin Pharma, generic)
- Fenofibrate (fenofibrate capsule – H2 Pharma)
- fenofibrate capsules and tablets (generic – multiple manufacturers)
- fenofibric acid tablets and capsules (generic – multiple manufacturers)
- Fenoglide® (fenofibrate tablets – Salix/Valeant, generic)
- Fibricor® (fenofibric acid tablets – Aralez Pharmaceuticals, generic)
- Lipofen® (fenofibrate capsules – Kowa Pharmaceuticals)
- Lofibra® (fenofibrate tablets and capsules – Teva Select Brands)
- TriCor® (fenofibrate tablets – AbbVie, generic)
- Triglide® (fenofibrate tablets – Shionogi)
- Trilipix® (fenofibric capsules, delayed-release – AbbVie, generic)

REVIEW DATE: 10/23/2019; selected revision 07/22/2020

OVERVIEW

Fenofibrate/fenofibric acid is a lipid regulating agents available in various oral formulations.[1-14] The products are indicated as an adjunct to diet:

- to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (total-C), triglycerides (TG) and apolipoprotein B (Apo B), and to increase high-density lipoprotein cholesterol (HDL-C) in adults with primary hypercholesterolemia or mixed dyslipidemia.
- for treatment of adults with hypertriglyceridemia.

A limitation of use is that the products have not been shown to reduce coronary heart disease morbidity and mortality in patients with type 2 diabetes mellitus.[1-14] The products have been studied for use in combination with other agents.[15,16] Also, many fenofibrate products are available, both brand and generic, and some have undergone reformulations.[17]

POLICY STATEMENT

This program has been developed to encourage the use of a Step 1 drug prior to the use of aa Step 2 drug. If the Step Therapy rule is not met for a Step 2 drug at the point of service, coverage will be determined by the Step Therapy criteria below. All approvals are provided for 1 year in duration.

Automation: A patient with a history of one Step 1 drug within the 130-day look-back period is excluded from step therapy.

Step 1: generic fenofibrate tablets (48 mg, 54 mg, 145 mg, and 160 mg), generic fenofibrate capsules (43 mg, 67 mg, 130 mg, 134 mg, and 200 mg), generic fenofibric acid tablets (35 mg and 105 mg), and generic fenofibric acid capsules (45 mg and 135 mg)

Step 2: Tricor, Antara, Triglide, Lipofen, Fenoglide, Trilipix, Fenofibrate, Fibricor, fenofibrate 40 mg, fenofibrate 120 mg, fenofibrate 50 mg, and fenofibrate 150 mg

CRITERIA

1. If the patient has tried one Step 1 product, authorization for a Step 2 product may be given.

2. No other exceptions are recommended.

REFERENCES

1. TriCor® tablets [prescribing information]. North Chicago, IL: AbbVie; November 2018.
2. Lofibra® tablets [prescribing information]. Horsham, PA: Teva Select Brands; January 2017.
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4. Antara® capsules [prescribing information]. Baltimore, MD: Lupin Pharma; April 2019.
5. Triglide® tablets [prescribing information]. Florham Park, NJ: Shionogi; July 2017.
6. Lipofen® capsules [prescribing information]. Montgomery, AL: Kowa Pharmaceuticals; May 2019.
7. Fenoglide® tablets [prescribing information]. Bridgewater NJ: Salix Pharmaceuticals; May 2019.
8. Trilipix® capsules, delayed-release [prescribing information]. North Chicago, IL: AbbVie; November 2018.
9. Fibricor® tablets [prescribing information]. Princeton, NJ: Aralez Pharmaceuticals; October 2016.
10. Fenofibrate capsules [prescribing information]. Baudette, MN: ANI Pharmaceuticals; January 2019.
11. Fenofibrate tablets [prescribing information]. Sunrise, FL: Cipla; June 2017.

12. Fenofibric acid delayed-release pellets [prescribing information]. Morgantown, WV: Mylan Pharmaceuticals; December 2016.
13. Fenofibric acid delayed release capsules [prescribing information]. Baltimore, MD: Lupin; June 2015.
14. Fenofibrate capsules [prescribing information]. Montgomery, AL: H2-Pharma; May 2014.
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16. McKeage K, Keating GM. Fenofibrate. A review of its use in dyslipidemia. *Drugs*. 2011;71(14):1917-1946.
17. Downing NS, Ross JS, Jackevicius CA, Krumholz HM. Avoidance of generic competition by Abbott Laboratories' fenofibrate franchise. *Arch Intern Med*. 2012;172(9):724-730.

PRIOR AUTHORIZATION POLICY

POLICY: Gamifant® (emapalumab-lzsg for intravenous injection – Sobi)

DATE REVIEWED: 12/18/2019

OVERVIEW

Gamifant is a fully human monoclonal antibody against interferon gamma (IFN-γ).[1] It is indicated for the treatment of adult and pediatric (newborn and older) patients with primary hemophagocytic lymphohistiocytosis (HLH) [also referred to as familial HLH] with refractory, recurrent, or progressive disease or intolerance with conventional HLH therapy. Per product labeling, Gamifant should be administered concomitantly with systemic dexamethasone and with prophylaxis for Herpes Zoster, *Pneumocystis jirovecii,* and fungal infections.

HLH is a syndrome characterized by signs and symptoms of extreme inflammation, caused by defects in cytotoxic function that lead to over-activation of the immune system.[2] The incidence is estimated at 1.2 cases per million individuals per year, but this is likely an underestimate.[3] Cytotoxic function is an important process in immune regulation; by inducing apoptosis in activated immune cells, effector cells (cytotoxic T cells or natural killer [NK] cells) terminate the immune response when appropriate. Deficiencies in cytotoxic function lead to hyper-inflammation as effector cells are unable to silence activated immune cells via apoptosis. Sustained hyper-inflammation leads to multi-organ damage, with the liver being most commonly affected.[2,3] HLH can be classified as primary or secondary. Primary HLH has a clear genetic cause, whereas secondary HLH is triggered by a concomitant infection or medical condition, such as Epstein-Barr Virus (EBV) infection, malignancy, or rheumatologic disorders.

IFN-γ has an important role in immune regulation and in HLH pathophysiology.[4,5] Pro-inflammatory effects of IFN-γ include macrophage activation, upregulation of antigen presentation pathways, and stimulation of cytokines including interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, and others. In healthy individuals, IFN-γ also exerts anti-inflammatory effects by activating cytotoxic T lymphocytes and NK cells, inducing apoptosis and silencing the immune response. In HLH, due to impaired activity of cytotoxic T cells and NK cells, INF-γ is unable to exert anti-inflammatory effects. Thus the pro-inflammatory effects are unbalanced, resulting in immune over-activation. Additionally, IFN-γ is thought to be hyper-secreted as a result of deficient cytotoxic activity.[1]

Guidelines

The HLH-2004 treatment protocol, developed by the Histiocyte Society, is the current standard of care for diagnostic and therapeutic guidelines.[6] To establish a diagnosis of HLH, patients must either have a molecular diagnosis consistent with HLH or must 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. All patients

should receive an initial 8 weeks of induction chemotherapy. Patients with secondary HLH may be able to stop chemotherapy (though it should be resumed if reactivation occurs); secondary HLH has a highly variable course and has been reported to sometimes resolve with resolution of the underlying disease.[3,6] By contrast, 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 6 months in duration. 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)** The patient has a diagnosis of hemophagocytic lymphohistiocytosis determined by at least one of the following (i or ii):
     - **i.** The 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)** Fasting triglycerides ≥ 265 mg/dL OR 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)** The 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

Gamifant 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.)

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

24. Gamifant® [prescribing information]. Waltham, MA: Sobi, Inc; November 2018.
25. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. *Blood*. 2011;118(15):4041-4052.
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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

40. 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:

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

165. Gattex® for injection, for subcutaneous use [prescribing information]. Lexington, MA: Shire/NPS Pharmaceuticals; May 2019.
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PRIOR AUTHORIZATION POLICY

POLICY: Gaucher Disease – Enzyme Replacement Therapy – Cerezyme® (imiglucerase for injection – Genzyme)

DATE REVIEWED: 03/25/2020

OVERVIEW

Cerezyme is an analogue of β-glucocerebrosidase produced via recombinant DNA technology in Chinese hamster ovary cells.[1] Cerezyme differs from human placental glucocerebrosidase by one amino acid at position 495. Cerezyme catalyzes the breakdown of glucocerebroside to glucose and ceramide.

Cerezyme 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]

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

41. Gaucher Disease, Type 1. 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.** Demonstration of deficient β-glucocerebrosidase activity in leukocytes or fibroblasts; OR
  - **ii.** Molecular genetic testing documenting glucocerebrosidase gene mutation; AND
- **B)** 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

Cerezyme 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.

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

167. Cerezyme® for injection [prescribing information]. Cambridge, MA: Genzyme Corporation; April 2018.
168. Burrow TA, Barnes S, and Grabowski GA. Prevalence and management of Gaucher disease. Pediatric Health, Medicine and Therapeutics. 2011;2:59-73

169. Cox T. Gaucher disease: clinical profile and therapeutic development. Biologics: Targets & Therapy. 2010;4:299-313
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PRIOR AUTHORIZATION POLICY

POLICY: Gaucher Disease – Enzyme Replacement Therapy – Elelyso® (taliglucerase for injection – Pfizer)

DATE REVIEWED: 03/25/2020

OVERVIEW

Elelyso is an analogue of β-glucocerebrosidase 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.

Elelyso is indicated for the treatment of patients with a confirmed diagnosis of Type 1 Gaucher disease.[1]

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

42. Gaucher Disease, Type 1. 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.** Demonstration of deficient β-glucocerebrosidase activity in leukocytes or fibroblasts; OR
  - **ii.** Molecular genetic testing documenting glucocerebrosidase gene mutation; AND
- **B)** 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

Elelyso 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.

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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177. Cox T. Gaucher disease: clinical profile and therapeutic development. Biologics: Targets & Therapy. 2010;4:299-313
178. Jmoudiak, M. and Futerman, AH. Gaucher disease: Pathological mechanisms and modern management. British Journal of Haematology. 2005;129(2):178–188
179. Grabowski GA. Lysosomal storage disease 1- phenotype, diagnosis, and treatment of Gaucher's disease. Lancet. 2008;372:1263-1271.
180. Zimran A. How I treat Gaucher disease. Blood. 2011;118:1463-1471.
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182. Baris HN, Cohen IJ, Mistry PK. Gaucher disease: The metabolic defect, pathophysiology, phenotypes and natural history. *Pediatr Endocrinol Rev*. 2014;12:72-81.

PRIOR AUTHORIZATION POLICY

POLICY: Gaucher Disease – Enzyme Replacement Therapy – Vpriv® (velaglucerase for injection – Shire Human Genetic Therapies)

DATE REVIEWED: 03/25/2020

OVERVIEW

Vpriv is an analogue of β-glucocerebrosidase 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.

Vpriv is indicated for long-term enzyme replacement therapy for patients with Type 1 Gaucher disease.[1]

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

43. Gaucher Disease, Type 1. 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.** Demonstration of deficient β-glucocerebrosidase activity in leukocytes or fibroblasts; OR
  - **ii.** Molecular genetic testing documenting glucocerebrosidase gene mutation; AND
- **B)** 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

Vpriv 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.

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

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184. Burrow TA, Barnes S, and Grabowski GA. Prevalence and management of Gaucher disease. Pediatric Health, Medicine and Therapeutics. 2011;2:59-73
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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

38. 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.

111. 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. Cerdelga™ capsules [prescribing information]. Waterford, Ireland: Genzyme; August 2018.

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

39. 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.

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

REFERENCES

31. Zavesca® [prescribing information]. South San Francisco, CA: Actelion Pharmaceuticals US Inc.; February 2014.
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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 Agonists – Central Precocious Puberty

- 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)

DATE REVIEWED: 09/18/2019; Selected revision, 05/13/2020

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 (SC) injection and both Lupron Depot-Ped and Triptodur are administered by intramuscular (IM) 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 GnRH agonists (Fensolvi, Lupron Depot-Ped, and Triptodur). All approvals are provided for the duration cited. 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 the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of a GnRH 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 GnRH 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 GnRH 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

GnRH agonists (Fensolvi, Lupron Depot-Ped, and Triptodur) 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.)

113. **Peripheral Precocious Puberty (also known as GnRH-independent precocious puberty)**.
    Children with peripheral precocious puberty do not respond to GnRH 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]).

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

REFERENCES

285. Lupron Depot-Ped® [prescribing information]. North Chicago, IL; AbbVie, Inc.; May 2017.
286. Triptodur™ [prescribing information]. Atlanta, GA: Arbor Pharmaceuticals, LLC; October 2018.
287. Fensolvi® [prescribing information]. Fort Collins, CO: Tolmar Pharmaceuticals, Inc; May 2020
288. 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.
289. 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.
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292. World Professional Association for Transgender Health (WPATH). Standards of Care for the health of transsexual, transgender, and gender non-conforming people (version 7). Available at: https://s3.amazonaws.com/amo_hub_content/Association140/files/Standards%20of%20Care%20V7%20-%202011%20WPATH%20%282%29%281%29.pdf. Accessed on May 8, 2020.
293. Rosenthal SM. Approach to the patient: transgender youth: endocrine considerations. *J Clin Endocrine Metab.* 2014;99:4379-4389.
294. Spack NP. Management of transgenderism. *JAMA*. 2013;309:478-484.

PRIOR AUTHORIZATION POLICY

POLICY: Gonadotropin-Releasing Hormone Agonists Implants

- Supprelin® LA (histrelin acetate subcutaneous implant – Endo Pharmaceuticals)
- Vantas® (histrelin acetate subcutaneous implant – Endo Pharmaceuticals)
- Zoladex® (goserelin acetate subcutaneous implant – TerSera Therapeutics)

DATE REVIEWED: 01/15/2020; Selected revision, 3/11/2020

OVERVIEW

Supprelin LA, Vantas, and Zoladex are gonadotropin-releasing hormone (GnRH) agonists implants.[1-4] Vantas and Zoladex are indicated for the palliative treatment of advanced prostate cancer.[1-3] Zoladex is also FDA-approved for use in combination with flutamide for the management of locally confined prostate cancer (3.6 mg and 10.8 mg implants).[2,3] In addition, Zoladex 3.6 mg is indicated for the management of endometriosis, for use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding, and for the palliative treatment of advanced breast cancer in pre- and perimenopausal women.[2] Supprelin LA is a GnRH agonist indicated for the treatment of children with central precocious puberty.[3] 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.

Guidelines

The National Comprehensive Cancer Network (NCCN) Prostate Cancer guidelines (version 4.2019 – August 19, 2019) 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.[5]

The NCCN Breast Cancer guidelines (version 3.2019 – September 6, 2019) does not note the use of Zoladex implants for advanced breast cancer.[6] However, the guidelines note that ovarian suppression with GnRH agonists (e.g., Zoladex) 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.

Central precocious puberty, also known as gonadotropin-dependent precocious puberty, is caused by early maturation of the hypothalamic-pituitary-gonadal axis.[7] 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 to review the use of GnRH agonists in pediatric patients with central precocious puberty (2009).[8] 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.[9] GnRH agonists are generally well-tolerated in children and adolescents.

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. **Prostate Cancer**. Approve for 1 year if the medication is prescribed by, or in consultation with, an oncologist.

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) The patient is ≥ 18 years of age; AND
   B) 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.

4. **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 health care practitioner who specializes in the treatment of women's health.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Supprelin LA, Vantas, and Zoladex 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.

115. 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 Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Vantas® Subcutaneous Implant [prescribing information]. Malvern, PA: Endo Pharmaceuticals Inc.; November 2019.
2. Zoladex® 3.6 mg Implant [prescribing information]. Lake Forest, IL: TerSera Therapeutics; February 2019.
3. Zoladex® 10.8 mg Implant [prescribing information]. Lake Forest, IL: TerSera Therapeutics; February 2019.
4. Supprelin® LA [prescribing information]. Malvern, PA Endo Pharmaceuticals Solutions Inc.; November 2019.
5. 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 January 7, 2020.
6. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 3.2019 – September 6, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 7, 2020.
7. Eugster EA. Treatment of central precocious puberty. *J Endo Soc*. 2019;3:965-972.
8. Carel JC, Eugster EA, Rogol A, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics*. 2009 Apr;123(4):e752-62.
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PRIOR AUTHORIZATION POLICY

POLICY: Gonadotropin-Releasing Hormone Agonists – Injectable Long-Acting Products

- Lupron Depot® (leuprolide acetate suspension for intramuscular [IM] injection – Abbott Laboratories)

- Lupaneta Pack® (leuprolide acetate for depot suspension; norethindrone acetate tablets co-packaged for intramuscular [IM] use and oral use, respectively – AbbVie Inc.)

DATE REVIEWED: 01/15/2020

OVERVIEW

This policy only includes the long-acting leuprolide acetate suspension products: Lupron Depot and Lupaneta Pack. Lupaneta Pack contains a combination pack of leuprolide acetate depot suspension for intramuscular (IM) injection and norethindrone 5 mg tablets (oral).[1,2] This policy does not cover the short-acting leuprolide products or other long-acting leuprolide products (e.g., Lupron, Lupron Depot-Ped). The indication(s) and dosing for Lupron Depot and Lupaneta Pack are in Table 1.

Table 1. Indications, Dosage and Administration for Lupron-Depot, Lupaneta.[1-5]

Products	Dosing and Administration	Indication(s)
Lupron Depot® (leuprolide acetate IM for depot suspension)	7.5 mg IM every 1 month 22.5 mg IM every 3 months 30 mg IM every 4 months 45 mg IM every 6 months	Prostate cancer: palliative treatment of advanced prostate cancer.
Lupron Depot® (leuprolide acetate IM for depot suspension)	3.75 mg IM every 1 month 11.25 mg IM every 3 months	Endometriosis: management, including pain relief and reduction of endometriotic lesions. Limitation of Use: Duration of use is limited due to concerns about adverse impact on bone mineral density. The initial treatment course of Lupron Depot (whether used alone or with norethindrone acetate add-back therapy) is limited to 6 months. A single retreatment course of not more than 6 months of Lupron Depot plus norethindrone acetate add-on therapy may be administered if symptoms recur after the initial course of treatment. Do not use Lupron Depot alone for retreatment. Use of Lupron Depot plus add-on therapy for longer than total of 12 months is not recommended. Uterine leiomyomata (Fibroids): preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata; taken with iron therapy. Recommended duration of therapy is up to 3 months.
Lupaneta Pack® (leuprolide acetate for IM depot suspension; norethindrone acetate oral tablets co-packaged)	3.75 mg IM every 1 month with norethindrone acetate 5 mg tablets 11.25 mg IM for 3 months with norethindrone acetate 5 mg tablets	Endometriosis: initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms. Limitation of Use: Duration of use is limited due to concerns about adverse impact on bone mineral density. The initial treatment course is limited to 6 months. A single retreatment course of not more than 6 months may be administered if symptoms recur after the initial course of treatment. Use of Lupaneta Pack for longer than total of 12 months is not recommended.

IM – Intramuscular.

Guidelines

Endometriosis

According to the American College of Obstetricians and Gynecologists (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).[6]

Abnormal Uterine Bleeding/Uterine Leiomyomata (Fibroids)
The 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.[7] 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.[8] GnRH agonists are noted as medications that can stop the menstrual cycle and shrink fibroids. GnRH analogues 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.[9] 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.[10]

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.[11] 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.[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, and various guidelines (e.g., guidelines from the National Comprehensive Cancer Center [NCCN]) discuss its use. The NCCN guidelines for Ovarian Cancer including Fallopian Tube Cancer and Primary Peritoneal Cancer (version 3.2019 – November 26, 2019) recommend leuprolide as a hormonal therapy option in various settings (e.g., adjuvant therapy, recurrence).[17] The NCCN guidelines for Breast Cancer (version 3.2019 – September 6, 2019) note that luteinizing hormone-releasing hormone agonists, such as leuprolide, can be used for ovarian suppression.[18] For this use, leuprolide should be given as monthly injections as the 3-month depots do not reliably suppress estrogen levels in all patients. 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 Adolescent and Young Adult Oncology (version 1.2020 – July 11, 2019)[19] note there are some data to suggest menstrual suppression with GnRH agonists may protect ovaries in young women with breast cancer before the initiation of chemotherapy. There are conflicting data regarding the beneficial effects of GnRH agonists on fertility preservation. The NCCN guidelines for Head and Neck Cancer (version 3.2019 – September 6, 2019) recommend the use of androgen receptor therapy (i.e., leuprolide, bicalutamide) for androgen receptor-positive, recurrent salivary gland tumors with distant metastases.[20]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Lupron-Depot and Lupaneta Pack. 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 Lupron Depot and Lupaneta Pack are recommended in those who meet the following criteria:

FDA-Approved Indications

14. **Prostate Cancer.** Approve Lupron Depot for 1 year if prescribed by, or in consultation with, an oncologist.

15. **Endometriosis.** Approve Lupron Depot or Lupaneta Pack for 1 year 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. **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).

16. **Uterine Leiomyomata (fibroids).** Approve Lupron Depot for 6 months.

Other Uses with Supportive Evidence

17. **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.

18. **Ovarian Cancer.** Approve Lupron Depot for 1 year if prescribed by, or in consultation with, an oncologist.

19. **Breast Cancer.** Approve Lupron Depot for 1 year if prescribed by, or in consultation with, an oncologist.

20. **Preservation of Ovarian Function/Fertility in Patients Undergoing Chemotherapy.** Approve Lupron Depot for 1 year if prescribed by, or in consultation with, an oncologist

21. **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.

22. **Abnormal Uterine Bleeding.** Approve Lupron Depot for 6 months.

23. **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) The patient has recurrent disease with distant metastases; AND
    B) The 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

Lupron Depot and Lupaneta Pack 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.)

116. **Hirsutism.** Patients with hirsutism, either idiopathic or due to polycystic ovarian syndrome (PCOS), have received long-acting leuprolide, usually 3.75 mg or 7.5 mg IM monthly.[21-23] Sometimes conjunctive therapy with estrogen replacement or oral contraceptives was used. Patients receiving long-acting leuprolide for up to 6 months experienced positive benefits such as decreases in the Ferriman-Gallwey scores, in hair growth rate and/or in the percentage hair growth rate.[21,22] The Endocrine Society guidelines (2008) 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.[24]

117. **Menstrual Migraine.** Therapies such as NSAIDs, triptans, and propranolol have been used for the treatment or prophylaxis of menstrual migraines.[25,26] A nonrandomized, 10-month prospective trial[27] assessed the effects of long-acting leuprolide 3.75 mg IM monthly in five women with severe menstrual migraines who were not responsive to prior treatment. Treatment led to a reduction in mean cumulative

monthly headache score. Also, patient global assessment of therapy was positive and a decrease in the use of analgesic medication for headache was noted. A review article notes that GnRH analogues 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.[28]

118. **Polycystic Ovarian Syndrome (PCOS).** Long-acting leuprolide has been used in women with PCOS.[29] Patients with PCOS receiving long-acting leuprolide 3.75 mg IM every 4 weeks plus an oral contraceptive for 6 months experienced a restoration of normal ovulatory cycles and a greater reduction in ovarian volume compared with women just receiving an oral contraceptive. PCOS guidelines from the Endocrine Society (2013)[30] and review articles[31,32] do not recommend this as a treatment modality.

119. **Premenstrual Syndrome (PMS).** Low-dose selective serotonin reuptake inhibitors (SSRIs) [e.g., fluoxetine, sertraline] are recommended as first-line agents for severe PMS.[33] Other first-line options for PMS include exercise, vitamin B6, combined contraceptive pills, and cognitive behavioral therapy. Use of GnRH analogues results in profound cycle suppression and elimination of PMS symptoms, but these agents should not be used routinely. It is recommended (sometimes) to aid in the diagnosis of PMS. Otherwise it is recommended only as a third-line treatment or for the most refractory patients.

120. 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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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

44. 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.)

51. Heavy Menstrual Bleeding <u>not</u> associated with Uterine Fibroids.
Oriahnn has been shown effective in reducing heavy menstrual bleeding only in women with uterine fibroids.[1]

52. 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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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

40. Endometriosis. Approve for the duration noted if the patient meets one of the following (A or B):

34. 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.

35. 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.)

121. 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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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.)

122. **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.

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

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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.

PRIOR AUTHORIZATION POLICY

POLICY: Growth Disorders – Growth hormone [somatropin]

- 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)

DATE REVIEWED: 2/5/2020; selected revision 4/8/2020

OVERVIEW

Indications for somatropin vary among these products. Somatropin is indicated for the following conditions:

1. Treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone;[1-7]
2. Treatment of idiopathic short stature, also called non-growth hormone deficient short stature, 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]
3. Replacement of endogenous growth hormone in adults with growth hormone deficiency (GHD);[1-7]
4. Treatment of growth failure in children with chronic kidney disease (CKD) up to the time of kidney transplantation;[4]
5. Treatment of patients with short stature associated with Noonan syndrome;[3]
6. Treatment of patients with growth failure or short stature associated with Prader Willi syndrome;[1,3,7]
7. Treatment of short stature or growth failure in children with short stature homeobox-containing gene (SHOX) deficiency;[2,6]
8. Treatment of growth failure or short stature in patients born small for gestational age (SGA) with no catch-up growth by age 2[1,7] to 4 years[2,3,6];
9. Treatment of short stature associated with Turner syndrome;[1-4,6,7]
10. Treatment of short bowel syndrome (SBS) in adult patients receiving specialized nutritional support;[8]
11. Treatment of human immunodefiency virus (HIV) infected patients with wasting or cachexia 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 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.[1-4,6,7,63]

Short Bowel Syndrome
Somatropin is indicated for the treatment of short SBS in adults receiving specialized nutritional support.[11] Therapy for more than 4 weeks has not been adequately studied.

Human Immunodeficiency Virus-Associated Wasting or Cachexia
Somatropin is indicated for the treatment of HIV-infected adults with wasting (loss of 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 will be required for Growth Hormone Deficiency in Adults or Transition Adolescents 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. For Adult and Transition Adolescent 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. This *Growth Hormone Prior Authorization Policy* document applies to the Standard Program.

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 patients who meet one of 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) The patient meets the following (i and either ii or iii):
      i. The patient has been evaluated by an endocrinologist; AND
      ii. The 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
      iii. The patient meets both of the following criteria (a and b):
         a) The 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) The 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).

         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).

   B) The patient has *undergone brain radiation or tumor resection* AND meets the following criteria (i and ii):
      i. The patient has been evaluated by an endocrinologist; AND
      ii. The patient meets at least ONE of the following criteria (a or b):
         a) The 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) The 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).

   C) The patient has *congenital hypopituitarism* AND meets the following criteria (i and ii):
      i. The patient has been evaluated by an endocrinologist; AND

ii. The patient meets at least ONE of the following criteria (a or b):
- **a)** The 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)** The 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.

D) The 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. The patient has been evaluated by an endocrinologist; AND

ii. 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)** The 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.

E) The 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 ≥ 4 cm/year in the most recent year.

B) *Adolescents between ≥ 12 years and ≤ 18 years of age.* The patient meets the following criteria (i and ii):
- **i.** Height has increased by ≥ 4 cm/year in the most recent year; AND
- **ii.** The epiphyses are open.

C) *Adolescents or young adults > 18 years of age.* The patient meets the following criteria (i, ii, and iii):
- **i.** Height has increased by ≥ 4 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 (defined as growth rate < 4 cm/year) 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)** The patient's baseline height is less than 1.2 percentile or a standard deviation score (SDS) < -2.25 for age and gender; AND
   - **C)** The 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)** The 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 ≥ 4 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). The patient meets the following criteria (i and ii):
     - **i.** Height has increased by ≥ 4 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). The patient meets the following criteria (i, ii, and iii):
     - **i.** Height has increased by ≥ 4 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) Patient has been evaluated by an endocrinologist; AND

B) The endocrinologist must certify that somatropin is not being prescribed for anti-aging therapy or to enhance athletic ability or for body building; AND

C) 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

D) The patient meets one of the following criteria (i, ii, or iii):

- **i.** The patient (adult or transition adolescent) has known mutations, embryopathic lesions, congenital or genetic defects, or structural hypothalamic-pituitary defects; [documentation required] OR
- **ii.** The patient meets the following criteria (a, b, and c):
  - **a)** The 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.** The 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: The 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) The patient has been off somatropin therapy for at least 1 month before retesting with a growth hormone stimulation test; AND

b) The 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.

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 been evaluated by an endocrinologist or a nephrologist; AND
   B) Patient has or had chronic kidney disease (CKD) as defined by an abnormal creatinine clearance.

   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) The patient has been evaluated by an endocrinologist; AND
   B) The patient's baseline height is less than the 5th percentile using a growth chart for children without Noonan syndrome.

   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 ≥ 2.5 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 ≥ 2.5 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 < 2.5 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 < 2.5 cm/year* The patient meets the following criteria (i and ii):
      i. The patient must be evaluated by an endocrinologist or in consultation with an endocrinologist; AND
      ii. This physician must certify that somatropin is not being used for anti-aging therapy or to enhance athletic performance/body building.

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 has been evaluated by an endocrinologist; AND
   D) The patient's baseline height is less than the 3rd percentile for age and gender.

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 ≥ 2.5 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 has been evaluated by an endocrinologist; AND
C) 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
D) The patient's baseline height is less than the 5th percentile for age and gender.

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 ≥ 4 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 ≥ 4 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 ≥ 4 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 ≥ 2.5 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 receiving specialized nutritional support (defined as a high carbohydrate, low-fat diet that is adjusted for individual patient requirements and preferences); AND

B) Patient is ≥ 18 years of age.

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)** The 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 recommended in circumstances that are listed in the Recommended Authorization Criteria (FDA-Approved Indications). For some of the following indications, authorization for coverage is not recommended because this indication is excluded from coverage in a typical pharmacy benefit. Note: This is not a level of evidence, but is a reason for exclusion from coverage. The following provides rationale for specific Exclusions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

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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PRIOR AUTHORIZATION POLICY

POLICY: Growth Disorders – Increlex® (mecasermin [rDNA origin] for subcutaneous injection – Ipsen Biopharmaceuticals/Hospira)

DATE REVIEWED: 10/16/2019

OVERVIEW

Increlex is indicated for the long-term treatment of growth failure in children with severe primary insulin-like growth factor-1 (IGF-1) deficiency (Primary IGFD) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH.[1] Severe Primary IGFD is defined by:

- Height standard deviation score (SDS) ≤ -3.0 and
- basal IGF-1 SDS ≤ -3.0 and
- normal or elevated GH

Increlex is given by subcutaneous (SC) 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 for GH for approved GH indications. Increlex is not indicated in secondary forms of IGF-1 deficiency, such as GH deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids and is not a substitute for GH (somatropin) therapy.[1] Thyroid and nutritional deficiencies should be corrected before initiating Increlex.

Disease Overview

IGF-1 is the principal hormonal mediator of growth hormone action.[3] Under normal circumstances, GH 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, which is homologous to the insulin 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 IGFD is a group of disorders characterized by decreased IGF production with normal or increased GH secretion.[2] Three distinct molecular abnormalities have been identified as causes of primary IGFD: 1) mutations or gene deletions of the GH receptor gene; 2) mutations affecting the post- GH receptor (GHR) 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 GH deficient, and do not respond adequately to exogenous GH treatment.[1-2] Once a diagnosis of severe primary IGFD 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 IGFD.[1] In these studies, 11% of the patients (n = 7) had GH 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 for change from pre-Tx*		<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

24. Severe Primary Insulin-Like Growth Factor-1 (IGF-1) Deficiency (Primary IGFD) 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 less than 1 Year. Approve for 1 year if the patient meets ALL of the following conditions (i, ii, iii, and iv):

- **i.** Height standard deviation score is ≤ -3.0 at baseline; AND
- **ii.** Patient has a basal IGF-1 level below the lower limits of the normal reference range for the reporting laboratory.
  Note: Reference ranges for IGF-1 vary among laboratories and are dependent upon age, gender, and puberty status; AND
- **iii.** Growth hormone concentration is normal or increased at baseline; AND
- **iv.** Increlex is prescribed by or in consultation with a pediatric endocrinologist.

B) Patient has been receiving Increlex for at least 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.
  Note: Patients are reviewed annually for growth rate; AND
- **ii.** The epiphyses are open.

25. Growth Hormone (GH) Gene Deletion in a Child who has Developed Neutralizing Antibodies to GH. 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 less than 1 Year. Approve if Increlex is prescribed by or in consultation with a pediatric endocrinologist.

B) Patient has been receiving Increlex for at least 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.
Note: Patients are reviewed annually for growth rate; AND

ii. The epiphyses are open.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Increlex 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. 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

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PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Cablivi® (caplacizumab-yhdp for injection, for intravenous or subcutaneous use)

DATE REVIEWED: 01/29/2020

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

Acquired thrombotic thrombocytopenic purpura (aTTP) is a rare disease characterized by microangiopathic hemolytic anemia and thrombocytopenia.[2-4] aTTP is caused by autoantibodies directed against ADAMTS13. 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.[1-3,5]

Guidelines/Recommendations

Cablivi has not been incorporated into guidelines. The British Committee for Standards in Hematology, along with other experts, published guidelines for the management of thrombotic thrombocytopenic purpura and related thrombotic microangiopathies in 2012.[6] Plasma exchange and glucocorticoids are recommended for the management of patients with aTTP. Plasma exchange removes the ultra-large vWF and autoantibodies and replenishes ADAMTS13, and immunosuppressants inhibit autoantibody formation.[2,5,6] 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]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Cablivi. 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. All approvals are provided for one course of treatment. 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

17. **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.** The patient is ≥ 18 years of age; AND
    - **J.** Cablivi was initiated in the inpatient setting in combination with plasma exchange therapy; AND
    - **K.** The patient is currently receiving at least one immunosuppressive therapy.
      Note: Examples include systemic corticosteroids, rituximab (or a rituximab product), cyclosporine, cyclophosphamide, mycophenolate mofetil, hydroxychloroquine, Velcade® [bortezomib for injection]); AND

L. If the patient has previously received Cablivi, he/she has not had more than two recurrences of aTTP while on Cablivi; AND
M. Cablivi is prescribed by, or in consultation with, a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Cablivi 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.)

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

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4. Joly BS, Coppo P, Veyradier A. Thrombotic thrombocytopenic purpura. *Blood.* 2017;129:2836-2846.
5. Scully M, Cataland SR, Peyvandi F, et al. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. *N Engl J Med*. 2019;380:335-346.
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PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Ceprotin® (protein C concentrate [human] injection for intravenous use – Baxalta/Shire)

REVIEW DATE: 10/02/2019

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. 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; molecular genetic testing is available at specialized laboratories but may not

be necessary to perform. The prevalence of severe protein C deficiency is approximately 1:500,000 to 1:750,000 in the general population.

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.[3] 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

41. Protein C Deficiency, Severe. Approve for 1 year if Ceprotin is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Ceprotin 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.)

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

196. Ceprotin® injection for intravenous use [prescribing information]. Lexington, MA: Baxalta/Shire; December 2018.
197. Protein C Deficiency. National Organization of Rare Disorders. Updated 2016. Available at: https://rarediseases.org/rare-diseases/protein-c-deficiency/. Accessed on June 10, 2019.
198. 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 June 10, 2019.

PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Coagadex® (coagulation Factor X [human] injection for intravenous use – BPL)

REVIEW DATE: 09/11/2019

OVERVIEW

Coagadex, a plasma-derived coagulation Factor X product, is indicated for use in adults and children with hereditary Factor X deficiency for: 1) routine prophylaxis to reduce the frequency of bleeding episodes; 2) on-demand treatment

and control of bleeding episodes; and 3) perioperative management of bleeding in patients with mild and moderate hereditary Factor X deficiency.[1]

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 Corifact.

Guidelines

The National Hemophilia Foundation Medical and Scientific Advisory Council has guidelines for the treatment of hemophilia and other bleeding disorders (revised April 2018).[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

45. 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

Coagadex 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.)

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

REFERENCES

199. Coagadex® injection for intravenous use [prescribing information]. Plainsboro, NJ: Noro Nordisk; November 2016.
200. Menegatti M, Peyvandi F. Treatment of rare factor deficiencies other than hemophilia. *Blood*. 2019;133(5):415-424.
201. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders (Revised April 2018). MASAC Document #253. Adopted on April 19, 2018. Available at: https://www.hemophilia.org/node/3675. Accessed on September 9, 2019.

PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Corifact® (Factor XIII Concentrate [human] injection for intravenous use – CSL Behring)

REVIEW DATE: 09/11/2019

OVERVIEW

Cortifact, a Factor XIII concentrate, is indicated for routine prophylactic treatment and perioperative management of surgical bleeding in adult and pediatric patients with congenital Factor XIII deficiency.[1]

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 April 2018).[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

46. 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

Corifact 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.)

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

REFERENCES

202. Corifact® injection for intravenous use [prescribing information]. Kankakee, IL: CSL Behring; September 2017.
203. Menegatti M, Peyvandi F. Treatment of rare factor deficiencies other than hemophilia. *Blood*. 2019;133(5):415-424.
204. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders (Revised April 2018). MASAC Document #253. Adopted on April 19, 2018. Available at: https://www.hemophilia.org/node/3675. Accessed on September 9, 2019.

PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Fibrinogen Products

- Fibryga® (fibrinogen [human] for intravenous use – Octapharma USA)
- RiaSTAP® (fibrinogen concentrate [human] for intravenous use – CSL Behring)

REVIEW DATE: 10/02/2019

OVERVIEW

Fibryga and RiaSTAP, human fibrinongen 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.

Disease Overview

Congenital fibrinogen deficiencies are caused by mutations in the *FGA*, *FGB*, and *FGG* genes.[3,4] These genes are responsible for creating the polypeptide chains which form the functional fibrinogen (also known as Factor I) hexamer. Afibrinogenemia and hypofibrinogenemia are known as Type I or quantitative deficiencies due to low or absent circulating fibrinogen levels. Afibrinogenemia is very rare (estimated prevalence 1:1,000,000) and is caused by homozygous null mutations. It is often diagnosed in infancy with prolonged umbilical cord bleeding, although later age of onset is possible. Hypofibrinogenemia is caused by heterozygous null mutation and is therefore likely much more prevalent than afibrinogenemia, although the exact incidence is difficult to determine because many patients are asymptomatic.

Dysfibrinogenemia, also known as Type II or qualitative deficiency, is characterized by normal levels of fibrinogen but low functional activity.[3,4] It is caused by missense mutations. Clinical presentation is widely variable and can range from asymptomatic to bleeding or even thromboembolism. Increased thromboembolic risk may be explained by inability of defective fibrinogen to bind thrombin, leading to elevated circulating thrombin levels. Additionally, abnormal fibrinogen may form a fibrin clot that is resistant to plasmin degradation.

Diagnosis is made by routine coagulation tests in addition to fibrinogen assays.[5] An accurate diagnosis is crucial to distinguish between quantitative/type I and qualitative/type II disorders and guide appropriate treatment. Treatment of fibrinogen deficiency in 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).[6,7] Fibrinogen concentrates are preferred over fresh frozen plasma or cryoprecipitate due to the ability for more precise dosing, less volume overload, and decreased risk of viral contamination.[3,6,7]

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 or RiaSTAP is recommended in those who meet the following criteria:

FDA-Approved Indications

47. 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

Fibrinogen 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.)

56. Concomitant Use of Fibryga and RiaSTAP. There are no data to support concomitant use of these products.

57. 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]

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

REFERENCES

205. RiaSTAP® for intravenous use [prescribing information]. Kankakee, IL: CSL Behring; October 2017.
206. Fibryga® for intravenous use [prescribing information]. Hoboken, NJ: Octapharma USA; July 2017.
207. 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 June 10, 2019.
208. 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 June 10, 2019.
209. 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 June 11, 2019.

210. Congenital afibrinogenemia. National Organization for Rare Disorders. Updated 2018. Available at: https://rarediseases.org/rare-diseases/afibrinogenemia-congenital/. Accessed on June 10, 2019.
211. Palla R, Peyvandi F, Shapiro AD. Rare bleeding disorders: diagnosis and treatment. *Blood.* 2015;125(13):2052-2061.

PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Reblozyl® (luspatercept-aamt for subcutaneous injection)

DATE REVIEWED: 11/13/2019; selected revision 04/15/2020

OVERVIEW

Reblozyl is an erythroid maturation agent indicated for the following conditions:[1]

1. Beta-thalassemia, for treatment of adults with anemia who require regular red blood cell (RBC) transfusions; AND
2. 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 red blood cell units over 8 weeks in adult patients with very low- to intermediate-risk disease.

Reblozyl is not indicated for use as a substitute for red blood cell transfusions in patients who require immediate correction of anemia. In the pivotal study evaluating Roblozyl 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), and deletion. 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 (Hb).[2] Patients with a severe form (beta-thalassemia major) become symptomatic due to low Hb 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 red blood cells in the blood with too much iron inside the cell. However, the number of white blood cells and platelets is normal. Supportive therapy may include transfusions and use of erythropoiesis-stimulating agents (ESAs). A red blood cell transfusion is given when the red blood cell count is low and signs or symptoms of anemia, such as shortness of breath or fatigue, occur. ESAs may be given to increase the number of mature red blood cells 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).

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 2.2020 – February 28, 2020) recommend Roblozyl in patients symptomatic anemia due to MDS, in patients 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.

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

48. 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 criteria (i, ii, and iii):
  - **i.** The 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)** Continuation of Therapy. Approve for 1 year if according to the prescriber, the patient has experienced a clinically meaningful decrease in transfusion burden.

49. Myelodysplastic Syndrome. 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.** The patient is ≥ 18 years of age; AND
  - **ii.** According to the prescriber, the patient has myelodysplastic syndromes with ring sideroblasts; AND
  - **iii.** The patient has very low- to intermediate-risk myelodysplastic syndromes, as determined by the prescriber.
    Note: This is determined using the International Prognostic Scoring System (IPSS); AND
  - **iv.** The patient does not have a confirmed mutation with deletion 5q (del 5q); AND
  - **v.** The patient currently requires blood transfusions, defined as at least two red blood cell units over the previous 8 weeks; AND
  - **vi.** The patient meets ONE of the following (a or b):
    - **a)** The 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)** Continuation of Therapy. Approve for 1 year if, according to the prescriber, the patient has experienced a clinically meaningful decrease in transfusion burden.

50. 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.** The 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.** The patient has very low- to intermediate-risk disease, as determined by the prescriber.
    Note: This is determined using the International Prognostic Scoring System (IPSS); AND
  - **iv.** The patient does not have a confirmed mutation with deletion 5q (del 5q); AND
  - **v.** The patient currently requires blood transfusions, defined as at least two red blood cell units over the previous 8 weeks; AND
  - **vi.** The patient meets ONE of the following (a or b):

a) The 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) Continuation of Therapy. 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

Reblozyl 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.)

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

212. Reblozyl® for subcutaneous injection [prescribing information]. Summit; NJ and Cambridge, MA: Celgene and Acceleron; November 2019.
213. National Organization for Rare Disorders (NORD). Beta thalassemia. Available at: https://rarediseases.org/rare-diseases/thalassemia-major//. Accessed on November 8, 2019.
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216. National Cancer Institute, National Institutes of Health. Myelodysplastic syndromes treatment. Updated October 30, 2019. Accessed on April 7, 2020. Available at: https://www.cancer.gov/types/myeloproliferative/patient/myelodysplastic-treatment-pdq.
217. 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/clinical.asp. Accessed on April 7, 2020.

PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Tretten® (coagulation Factor XIII A-Subunit [recombinant] injection for intravenous use – NovoNordisk)

REVIEW DATE: 09/11/2019

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.[3] 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 April 2018).[2] 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

51. 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

Tretten 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.)

60. Congenital Factor XIII B-Subunit Deficiency. Tretten will not work in patients who only lack Factor XIII-B subunit.[1,2]

61. 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. Tretten® injection for intravenous use [prescribing information]. Plainsboro, NJ: Noro Nordisk; November 2016.
219. Menegatti M, Peyvandi F. Treatment of rare factor deficiencies other than hemophilia. *Blood*. 2019;133(5):415-424.
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PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Vonvendi® (von Willebrand factor [recombinant] injection for intravenous use – Baxalta)

REVIEW DATE: 09/11/2019

OVERVIEW

Vonvendi, a recombinant von Willebrand factor, is indicated for use in adults ≥ 18 years of age diagnosed with von Willebrand disease for 1) on-demand treatment and control of bleeding episodes; and 2) 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 vonWillebrand disease include desmopressin either paraenterally or by a highly concentrated nasal spray (Stimate), Vonvendi, or plasma-derived Factor VIII product that contain von Willebrand Factor.

Guidelines

The National Hemophilia Foundation Medical and Scientific Advisory Council has guidelines for the treatment of hemophilia and other bleeding disorders (revised April 2018).[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 patient if the agent is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Vonvendi 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.)

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

221. Vonvendi® injection for intravenous use [prescribing information]. Lexington, MA: Baxalta US; February 2019.
222. 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.
223. 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.
224. MASAC (Medical and Scientific Advisory Council) recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders (Revised April 2018). MASAC Document #253. Adopted on April 19, 2018. Available at: https://www.hemophilia.org/node/3675. Accessed on June 7, 2019.
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PRIOR AUTHORIZATION POLICY

POLICY: Hemophilia – Eptacog Products

- NovoSeven® RT (Coagulation Factor VIIa [recombinant] for intravenous use – Novo Nordisk)

REVIEW DATE: 10/02/2019

OVERVIEW

NovoSeven RT is indicated for treatment of bleeding episodes and perioperative management in adults and children with hemophilia A or B with inhibitors, congenital Factor VII deficiency, and Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets.[1] It is also indicated for treatment of bleeding episodes and perioperative management in adults with acquired hemophilia. It is produced by recombinant technology in baby hamster kidney cells. Exogenous viruses are removed through a chromatographic purification process. No human serum or other proteins are used in the production or formulation of NovoSeven RT. The half-

life of NovoSeven RT is short (approximately 2 to 3 hours in patients with hemophilia A, hemophilia B, or congenital Factor VII deficiency), therefore frequent dosing is often required.

Disease Overview

Hemophilia A is an X-linked bleeding disorder caused by a deficiency in coagulation Factor VIII.[2] The birth prevalence of hemophilia A in the US is approximately 1:6,500 live male births. **Hemophilia B**, caused by deficiency in Coagulation Factor IX, is clinically indistinguishable from hemophilia A and is also inherited in an X-linked manner.[3] The birth prevalence is approximately 1:30,000 live male births. Bleeding episodes are treated with plasma-derived or recombinant Factor VIII or Factor IX concentrates. These agents are also given prophylactically for individuals with severe disease.

Approximately 30% of patients with severe hemophilia A and 1 to 3% of patients with severe hemophilia B develop alloimmune inhibitors (antibodies) to Factor VIII or Factor IX concentrate.[2,3] In **acquired hemophilia A**, individuals who were not born with hemophilia develop inhibitors to endogenous Factor VIII.[4] Certain conditions, including cancer, lupus erythematosus, and other autoimmune disorders, may predispose patients to development of acquired hemophilia A. In both acquired and congenital hemophilia, presence of inhibitors at high titers makes the factor replacement ineffective, and alternative "bypassing" agents are needed to promote hemostasis. Examples of commercially available bypassing agents include NovoSeven RT, as well as FEIBA® (anti-inhibitor coagulant complex for intravenous use).[5] Hemlibra® (emiczumab-kxwh for subcutaneous use) is a monoclonal antibody that mimics the action of Factor VIII and therefore is only indicated in hemophilia A.

Glanzmann's thrombasthenia (GT) is a genetic disorder of the glycoprotein IIb/IIIa complex on the platelet surface, which results in faulty platelet aggregation and diminished clot retraction.[6] The exact incidence is unknown but is estimated at approximately 1:1,000,000 individuals. Most individuals are diagnosed before 5 years of age. Prophylactic therapy is not needed, but treatment is necessary for surgical procedures and to control acute bleeding episodes. Platelet transfusion is considered standard therapy if local measures are inadequate to control bleeding. NovoSeven RT has been successfully used in patients who are refractory to platelet transfusions or to avoid the need for transfusion. **Congenital Factor VII deficiency** is a rare autosomal recessive disorder affecting an estimated 1:300,000 to 1:500,000 individuals.[7,8] NovoSeven RT is the standard treatment for this condition.

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.[9] 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.[10-12]

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.[2] NovoSeven RT is supported as a treatment option for inherited hemophilia A or B with inhibitors, acquired hemophilia A, and Factor VII deficiency (Glanzmann's thrombasthenia is not addressed in the guidelines). MASAC recommendations (2013) also state that NovoSeven RT and FEIBA have demonstrated efficacy and safety for prophylactic use for patients with inhibitors in hemophilia A and hemophilia B.[13]

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

52. Congenital Factor VII Deficiency. Approve for 1 year if NovoSeven RT is prescribed by or in consultation with a hemophilia specialist.

53. Glanzmann's Thrombasthenia. Approve for 1 year if NovoSeven RT is prescribed by or in consultation with a hematologist.

54. Hemophilia A, Acquired. Approve for 1 year if NovoSeven RT is prescribed by or in consultation with a hemophilia specialist.

55. Hemophilia A with Inhibitors. Approve for 1 year if NovoSeven RT is prescribed by or in consultation with a hemophilia specialist.

56. Hemophilia B with Inhibitors. Approve for 1 year if NovoSeven RT is prescribed by or in consultation with a hemophilia specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

NovoSeven RT 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.)

63. 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.[14,15] 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.[16]

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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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)

DATE REVIEWED: 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

57. 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

Factor IX 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.)

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

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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.
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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)

DATE REVIEWED: 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

58. 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

Factor VIII 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.)

66. 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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245. Esperoct® lyophilized powder for solution for intravenous use [prescribing information]. Plainsboro, NJ: Novo Nordisk; October 2019.
246. Advate® lyophilized powder for reconstitution for intravenous injection [prescribing information]. Westlake Village, CA: Baxalta/Shire; December 2018
247. Kovaltry® lyophilized powder for solution for intravenous injection [prescribing information]. Whippany, NJ: Bayer HealthCare; March 2016.
248. Afstyla® lyophilized powder for solution for intravenous injection [prescribing information]. Kankakee, IL: CSL Behring; December 2019.
249. Helixate® FS lyophilized powder for reconstitution for intravenous use [prescribing information]. Kankakee, IL and Whippany, NJ: CSL Behring and Bayer HealthCare; May 2016.
250. Kogenate® FS lyophilized powder for reconstitution for intravenous use [prescribing information]. Whippany, NJ: Bayer HealthCare; May 2016.
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253. Novoeight® lyophilized powder for solution for intravenous injection [prescribing information]. Plainsboro, NJ: Novo Nordisk; November 2018.
254. Nuwiq® lyophilized powder solution for intravenous injection [prescribing information]. Hoboken, NJ: Octapharma; July 2017.
255. Recombinate™ lyophilized powder for reconstitution for injection [prescribing information]. Lexington, MA: Baxalta; June 2018.
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259. Monoclate-P® for intravenous use [prescribing information]. Kankakee, IL: Aventis Behring; February 2014.
260. Alphanate® for intravenous injection [prescribing information]. Los Angeles, CA: Grifols; June 2018.
261. Humate-P® lyophilized powder for reconstitution for intravenous use [prescribing information]. Kankakee, IL: CSL Behring; September 2017.
262. Koāte for intravenous injection [prescribing information]. Fort Lee, NJ and Research Triangle Park, NC: Kedrion Biopharmaand Grifols; June 2018.
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PRIOR AUTHORIZATION POLICY

POLICY: Hemophilia – FEIBA® (anti-inhibitor coagulant complex for intravenous use – Takeda)

REVIEW DATE: 10/02/2019

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.[1,2] FEIBA is produced from pooled human plasma.[1]

FEIBA is the only commercially available activated prothrombin complex concentrate. Prothrombin complex concentrates are commercially available, and each product has unique pharmacology and labeled use. Profilnine® SD (Factor IX complex for intravenous use) is a three-factor prothrombin complex concentrate containing Factors II, IX, and X, with minimal levels of Factor VII.[3] It is indicated only in hemophilia B. Kcentra® (prothrombin complex concentrate [human] for intravenous use) is a four-factor prothrombin complex concentrate containing inactivated forms of Factors II, VII, IX, and X.[4] Kcentra is labeled for urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist (e.g, warfarin) therapy in adults with acute major bleeding or need for an urgent surgery or invasive procedure.

Disease Overview

Hemophilia A is an X-linked bleeding disorder caused by a deficiency in coagulation Factor VIII.[5] The birth prevalence of hemophilia A in the US is approximately 1:6,500 live male births. **Hemophilia B**, caused by deficiency in coagulation Factor IX, is clinically indistinguishable from hemophilia A and is also inherited in an X-linked manner.[6] The birth prevalence is approximately 1:30,000 live male births. Bleeding episodes are treated with plasma-derived or recombinant Factor VIII or Factor IX concentrates. These agents are also given prophylactically for individuals with severe disease.

Approximately 30% of patients with severe hemophilia A and 1 to 3% of patients with severe hemophilia B develop alloimmune inhibitors (antibodies) to Factor VIII or Factor IX concentrate.[5,6] Presence of inhibitors at high titers makes the factor replacement ineffective, and alternative "bypassing" agents are needed to promote hemostasis. FEIBA acts as a bypassing agent by multiple mechanisms which are not fully understood; one major mechanism is supplying activated Factor X, which is normally produced by activated Factors VIII and IX in healthy individuals.[7] Other bypassing agents include NovoSeven RT® (coagulation Factor VIIa [recombinant] for intravenous use) and Hemlibra® (emiczumab-kxwh for subcutaneous use). Hemlibra is a monoclonal antibody that mimics the action of Factor VIII and therefore is only indicated in hemophilia A.[8]

Guidelines

The National Hemophilia Foundation (NHF) Medical and Scientific Advisory Council (MASAC) has recommendations concerning products used for the treatment of hemophilia, as well as guidelines specific to treatment of hemophilia patients with inhibitors (2018 and 2013, respectively).[2,9] FEIBA is supported in these guidelines and noted to be indicated for use in hemophilia patients only when an inhibitor is present.

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of FEIBA. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by an Express Scripts clinician (i.e., Medical Director or Pharmacist). 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

59. Hemophilia A with Inhibitors. Approve for 1 year if FEIBA is prescribed by or in consultation with a hemophilia specialist.

60. Hemophilia B with Inhibitors. Approve for 1 year if FEIBA is prescribed by or in consultation with a hemophilia specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

FEIBA 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.)

67. 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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PRIOR AUTHORIZATION POLICY

POLICY: Hemophilia – Hemlibra® (emicizumab-kxwh injection for subcutaneous use – Genentech/Roche/Chugai)

REVIEW DATE: 10/02/2019

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 adult and pediatric patients ages newborn and older with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors.[1] The recommended dose 3 mg/kg by subcutaneous injection once weekly (QW) for the first 4 weeks, followed by a maintenance dose of 1.5 mg/kg QW; 3 mg/kg once every 2 weeks; or 6 mg/kg once every 4 weeks. Hemlibra bridges activated Factor IX and Factor X to restore the function of missing activated Factor VIII that is required for effective hemostasis.

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

The National Hemophilia Foundation Medical and Scientific Advisory Committee (MASAC) [updated April 2018] states that Hemlibra prevents or reduces bleeding in patients with hemophilia A and inhibitors.[2] MASAC also published a document regarding the recommendations on the use and management of emicizumab-kxwh (Hemlibra) for hemophilia A with and without inhibitors.[6] Patients both with and without inhibitors should consider Hemlibra therapy. However, based on the clinical trial data, any patient with hemophilia A with an inhibitor who is having frequent bleeding episodes and is on either episodic therapy or bypassing agent prophylaxis will likely derive significant benefit from Hemlibra. Patients receiving bypassing agent prophylaxis with a few bleeding episodes could considered switching to Hemlibra due to factors such as a reduced burden of administration. Infants should be considered for prophylaxis with Hemlibra at any time after birth given the increased risk of intracranial hemorrhage prior to initiation of Factor VIII prophylaxis. It should be noted, however, that data are limited in patients < 6 months of age and the pharmacokinetic exposure is likely to be lower compared with older infants and children.

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 in 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

42. Hemophilia A. Approve for 1 year if the patient meets the following criteria (A and B):
N) The agent is prescribed by or in consultation with a hemophilia specialist; AND
O) The patient is using Hemlibra for routine prophylaxis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Hemlibra 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.)

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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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

36. 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.

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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

61. 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:

68. 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.

69. 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.

70. 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]

71. 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).

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

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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.

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

62. 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.

63. 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.

64. 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.

65. 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.

66. 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

67. 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.

68. 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 Vosevi is not recommended in the following situations:

73. 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).

74. Hepatitis C Virus (HCV) [any genotype], Combination with Any Other Direct-Acting Antivirals. Mavyret provides a complete antiviral regimen.

75. 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.

76. 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]

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
280. Mavyret™ tablets [prescribing information]. North Chicago, IL: AbbVie; May 2020.
281. 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.

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

69. 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

70. Other Systemic Viral Infections. Approve for 1 year.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of ribavirin 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

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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.
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PRIOR AUTHORIZATION POLICY

POLICY: Hepatitis C – Sovaldi® (sofosbuvir tablets and oral pellets – Gilead)

REVIEW DATE: 03/25/2020

OVERVIEW

Sovaldi is a hepatitis C virus (HCV) nucleotide analog non-serine (NS)5B polymerase inhibitor indicated for the treatment of genotype 1, 2, 3 or 4 chronic HCV infection as a component of a combination antiviral treatment.[1] Sovaldi is also indicated in pediatric patients ≥ 3 years of age with genotype 2 or 3 chronic HCV infection without cirrhosis or with compensated cirrhosis in combination with ribavirin. Sovaldi is a direct acting antiviral agent (DAA) against HCV and an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication.[1] Sovaldi is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. The place in therapy for Sovaldi has greatly lessened or is non-existent in some cases due to the availability of other DAAs with greater efficacy for many genotypes. However, Sovaldi is the only DAA indicated in pediatric patients with genotype 2 or 3 chronic HCV.

Dosing

The recommended dose of Sovaldi tablets is one 400 mg tablet taken orally once daily (QD) with or without food. 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 (WBR) or peginterferon and ribavirin (PR) for the treatment of chronic HCV in adults. Regimens with Sovaldi + PR or Sovaldi + WBR 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 + WBR is indicated in pediatric patients with genotype 2 or 3 chronic HCV and has a unique role in such patients. Table 2 provides pediatric dosing.

Daklinza® (daclatasvir tablets) is indicated in combination with Sovaldi for the treatment of genotypes 1 and 3 HCV in adults.[12] Table 1 describes the approved regimens for Daklinza + Sovaldi in adults.

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

Table 2. Daklinza + Sovaldi Treatment Regimens (Adults).[12]

	Patient Population	Treatment and Duration
Genotype 1	No Cirrhosis	Daklinza + Sovaldi x 12 weeks
	Compensated (Child-Pugh A) Cirrhosis	
	Post-Transplant	Daklinza + Sovaldi + ribavirin x 12 weeks
	Decompensated (Child-Pugh B or C) Cirrhosis	
Genotype 3	No Cirrhosis	Daklinza + Sovaldi x 12 weeks
	Compensated (Child Pugh A) Cirrhosis	Daklinza + Sovaldi + ribavirin x 12 weeks
	Decompensated (Child-Pugh B or C) Cirrhosis	
	Post-Transplant	

Guidelines

Please refer to the *Hepatitis C Virus Direct-Acting Antivirals Therapy Class Summary* for a summary of the American Association for the Study of Liver Diseases (AASLD) guidelines.[11] For the most up-to-date information always consult the guidelines. The guidelines generally prefer one of the many fixed-dose combinations in the majority of patients with HCV. Sovaldi still has a small role in combination with Daklinza in patients with Genotype 2 or 3 HCV with decompensated cirrhosis. Currently, Sovaldi + ribavirin remains the only FDA-approved DAA for children 3 through 11 years with genotype 2 or 3 infection. However, recent clinical trials evaluating weight-based dosing of Epclusa®

(sofosbuvir/velpatasvir tablets) and Mavyret® (glecaprevir/pibrentasvir) are expected to lead to FDA approval for children aged 3 through 11 years. The HCV guidance panel recommends awaiting approval of a pangenotypic regimen unless there is a compelling need for immediate antiviral treatment of children aged 3 through 11 years with genotype 2 or 3 infection.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Sovaldi. Criteria for whom to treat are based on the guidance issued by American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA), FDA-approved indications, clinical data, and expert review. Successful treatment of HCV results in sustained virologic response (SVR) and is expected to benefit nearly all chronically infected persons. Evidence clearly supports treatment in all HCV-infected individuals, except those with limited life expectancy (< 12 months) due to non-liver-related comorbid conditions. Approval durations differ by baseline characteristics. Because of the specialized skills required for evaluation and diagnosis of patients treated with Sovaldi as well as the monitoring required for adverse events (AEs) and efficacy, approval requires Sovaldi 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 Sovaldi is recommended in those who meet the following criteria:

FDA-Approved Indications

37. Chronic Hepatitis C Virus (HCV) Genotype 1, Adults. Approve for 12 weeks if the patient meets the following criteria (A, B, and C):

- **i.** The patient is ≥ 18 years of age; AND
- **ii.** Sovaldi is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician; AND
- **C)** Sovaldi will be prescribed in combination with Daklinza (daclatasvir tablets) AND the patient meets one of the following criteria (i, ii, or iii):
  - **i.** The patient does not have cirrhosis; OR
  - **ii.** The patient has compensated cirrhosis (Child-Pugh A); OR
  - **iii.** The patient has decompensated cirrhosis (Child Pugh B or C) AND Sovaldi will be prescribed in combination with Daklinza (daclatasvir tablets) AND ribavirin; OR

43. 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)** The patient is ≥ 3 years of age; AND
- **B)** Sovaldi is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician; AND
- **C)** Sovaldi will be prescribed in combination with ribavirin; AND
- **D)** The 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].

44. 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)** The patient is ≥ 3 years of age; AND
- **B)** Sovaldi is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician; AND
- **C)** Sovaldi will be prescribed in combination with ribavirin; AND
- **D)** The 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].

45. Chronic Hepatitis C Virus (HCV) Genotype 3, Adults. Approve for 12 weeks if the patient meets the following criteria (A, B, and C):
- **A)** The patient is ≥ 18 years of age; AND
- **B)** Sovaldi is prescribed by or in consultation with a gastroenterologist, hepatologist, infectious diseases physician, or a liver transplant physician; AND
- **C)** Sovaldi is prescribed in combination with Daklinza (daclatasvir tablets) AND the patient meets ONE of the following (i or ii):
  - **i.** The patient does not have cirrhosis; OR
  - **ii.** The patient has cirrhosis (this includes patients with compensated [Child-Pugh A] OR decompensated [Child-Pugh B or C] cirrhosis) AND Daklinza (daclatasvir tablets) and Sovaldi will be prescribed in combination with ribavirin.

Other Uses with Supportive Evidence

4. Recurrent Hepatitis C Virus (HCV) Post-Liver Transplantation, Genotypes 1, 2, and 3. Approve for 12 weeks 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 recurrent HCV after a liver transplantation; AND
- **C)** Sovaldi 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 a liver transplant physician; AND
- **D)** Sovaldi is prescribed in combination with Daklinza (daclatasvir tablets) AND ribavirin.

5. 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

Sovaldi 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. **HCV (any genotype), Combination use with Direct-Acting Antivirals (DAAs) Other than Daklinza or ribavirin.**

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.[11] 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] Sovaldi should be administered with PR, ribavirin, or Daklinza, and if the components recommended for use with Sovaldi are discontinued, Sovaldi should also be discontinued.[1,11] Monotherapy with a DAA is not recommended in any situation for patients with HCV.[11]

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

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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

71. **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.

72. **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.

73. **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.

74. **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
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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

75. 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.

76. 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

77. 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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PRIOR AUTHORIZATION POLICY

POLICY: Hepatitis C – Zepatier® (grazoprevir/elbasvir tablets – Merck)

REVIEW 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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HEPATITIS C GUIDELINE OVERVIEW FOR PRIOR AUTHORIZATION POLICIES

UPDATED: August 20, 2015

OVERVIEW OF GUIDELINES

The American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA)/International Antiviral-Society-UAS (IAS-USA) web-based recommendations for testing, managing, and treating hepatitis C were last updated August 7, 2015.[1] The guidance will be updated as new information becomes available and should be consulted for the most up-to-date information. The recommendations are based on evidence and reflect the best possible management for a given patient and

a given point of disease progression. The recommendations are graded with regard to the level of evidence (I through III) and strength of evidence (A through C). The level of evidence for each patient group varies, as does the strength of the recommendation, and is graded as such. A regimen classified as "recommended" is favored in most patients, a regimen classified as "alternative" is optimal in a particular subset of patients within a category. When a treatment is clearly inferior or is deemed to be harmful, it is classified as "not recommended". The guidance is not supported by pharmaceutical companies or other commercial interests. The guidance may recommend off-label use of certain drugs.

Below is a brief summary of the recommendations.

Assessing Fibrosis Stage

The severity of liver disease associated with chronic HCV infection is a key factor in determining the initial and follow-up evaluation of patients.[1] A live biopsy can provide an objective, semi-quantitative information regarding the amount and patterns of collagen or scar tissue in the liver that can assist with treatment and monitoring plans. The Metavir fibrosis score (F0 to F4) and the Ishak fibrosis score (0 to 6) are commonly used to score the amount of hepatic collagen. A liver biopsy can also help assess the severity of liver inflammation, or of hepatic steatosis, and help exclude competing causes of liver injury. However, the procedure has a low, but real risk of complications, and sampling artifact makes its serial use in most patients less desirable. Non-invasive methods frequently used to estimate liver disease severity include a liver-directed physical exam (normal in most patients), routine blood tests (e.g., serum alanine aminotransferase [ALT] and aspartate aminotransferase [AST], albumin, bilirubin, international normalized ratio [INR] levels, and complete blood counts with platelets), serum fibrosis market panels, liver imaging (e.g., ultrasound, computed tomography scan), and transient elastography. Simple blood tests (e.g., serum AST-to-platelet ratio index. An accurate assessment of fibrosis is very important in assessing the urgency for treatment. The degree of hepatic fibrosis is one of the most robust prognostic factors used to predict disease progression and clinical outcomes.[1] Liver biopsy is the diagnostic standard; however, sampling error and observer variability limit test performance, particularly when inadequate sampling occurs. In addition, the test is invasive and minor complications are common, limiting patient and practitioner acceptance. Serious complications such as bleeding, although rare, are well-recognized. Non-invasive tests to stage the degree of fibrosis in patients with chronic hepatitis C virus (HCV) infection include models incorporating indirect serum biomarkers (routine tests), direct serum biomarkers (components of the extracellular matrix produced by activated hepatic stellate cells), and vibration-controlled transient liver elastography. No single method is recognized to have high accuracy alone and each test must be interpreted carefully. A recent publication of the Agency for Healthcare Research and Quality (AHRQ) found evidence in support of a number of blood tests; however, at best they are only moderately useful for identifying clinically significant fibrosis or cirrhosis. Vibration-controlled transient liver elastography is a non-invasive way to measure liver stiffness and correlates well with measurement of substantial fibrosis or cirrhosis in patients with chronic HCV infection. A cutoff value of 8.7 kPa correlates with Metavir F2 or higher fibrosis stage; > 9.5 kPa with F3; and ≥ 14.5 or higher kPa with F4 or cirrhosis. Importantly, the measurement range overlaps between stages.

According to the guidelines, the most efficient approach to fibrosis assessment is to combine direct biomarkers and vibration-controlled transient liver elastography. A biopsy should be considered for any patient who has discordant results between the two methods that would affect clinical decision making.
Alternatively, if direct biomarkers or vibration-controlled transient liver elastography are not available, the aspartate aminotransferase-to-platelet ratio index (APRI) or fibrosis-4 index (FIB-4) can help identify those most likely to have F3 or F4 fibrosis stage. An APRI > 2.0 or FIB-4 > 3.25 has a high specificity for advanced fibrosis or cirrhosis, although neither test is sensitive enough to rule out substantial fibrosis if values are below these thresholds. Biopsy should be considered in those in whom more accurate fibrosis

staging would impact treatment decisions. Individuals with clinically evident cirrhosis do not require additional staging (biopsy or noninvasive assessment).

Who to Treat

The AASLD recommends treatment for all patients with chronic HCV infection, except those with a short life expectancy owing to comorbid conditions (Class I, Level A).[1] According to the AASLD successful HCV treatment results in sustained virologic response (SVR), which is tantamount to virologic cure, and as such, is expected to benefit nearly all chronically infected persons.[1] Evidence clearly supports treatment in all HCV-infected persons, except those with limited life expectancy (< 12 months) due to non–liver-related comorbid conditions. Immediate treatment is assigned the highest priority for those patients with advanced fibrosis (Metavir stage F3), those with compensated cirrhosis (Metavir stage F4), liver transplant recipients, and patients with severe extrahepatic hepatitis C. Based on available resources, immediate treatment should be prioritized as necessary so that patients at high risk for liver-related complications are given high priority. Based on available resources, immediate treatment should be prioritized as necessary so that patients at high risk for liver-related complications and severe extrahepatic hepatitis C complications are given high priority. The most immediate and high-impact benefits of SVR will be realized by populations that are at the highest risk for liver-related complications due to progressive liver disease (Metavir F3 or F4) and transplant recipients or those with clinically severe extrahepatic manifestations. Other populations at high risk for liver disease progression (Metavir F2) or with substantial extrahepatic manifestations are also expected to garner appreciable benefits, although the time course for realizing these benefits may be more protracted. SVR will also remove the risk of further transmission. Treatment of individuals at high-risk to transmit HCV to others may yield long-term future benefits from decreased transmission and a potential decrease in HCV disease prevalence. The guidelines also cite recent reports suggesting that initiating therapy in patients with lower stages of fibrosis may extend the benefits of SVR. Table 1 provides an overview of situations in which HCV treatment is most likely to provide the most immediate and impactful benefits.

Table 1. AASLD/IDSA/IAS-USA: Settings of Liver-Related Complications and Extrahepatic Disease in Which HCV Treatment is Most Likely to Provide the Most Immediate and Impactful Benefits.[1]

Highest Priority	**High Priority**	**Elevated Risk of Transmission**[†] [All Class IIa, Level C]
Advanced fibrosis (Metavir F3) [Class I, Level A]	Fibrosis (Metavir F2) [Class I, Level B]	MSM high-risk sexual practice
Compensated cirrhosis (Metavir F4) [Class I, Level A]	HIV-1 co-infection [Class I, Level B]	Active IDUs
Organ transplant recipients [Class I, Level B]	HBV co-infection [Class IIa, Level C]	Incarcerated persons
Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (e.g., vasculitis) [Class I, Level B]	Other co-existent liver disease (e.g., NASH) [Class IIa, Level C]	Long-term hemodialysis
Proteinuria, nephrotic syndrome, membranoproliferative glomerularnephritis [Class IIa, Level B]	Debilitating fatigue Type 2 diabetes [Class IIa, Level B]	HCV-infected women of child-bearing potential wishing to get pregnant
	Porphyria cutanea tarda [Class IIb, Level C]	
		HCV infected health care workers who perform exposure-prone procedures

AASLD – American Association for the Study of Liver Diseases; IDSA – Infectious Diseases Society of America; IAS-USA – International Antiviral Society USA; HCV – Hepatitis C virus; HIV – Human immunodeficiency virus; HBV – Hepatitis B virus; NASH – Non-alcoholic steatohepatitis; [†] Patients at substantial risk of transmitting should be counseled on ways to decrease transmission and minimize the risk of re-infection; MSM – Men who have sex with men; IDUs – Injection drug users.

Patients with Advanced Liver Disease (Metavir F3 or F4). For individuals with advanced liver disease (Metavir stage F3 or F4), the risk of developing complications of liver disease such as hepatic decompensation or hepatocellular carcinoma (HCC) is substantial and may occur in a relatively short timeframe. Many studies have demonstrated that hepatitis C therapy and attaining SVR in patients with advanced liver disease results in dramatic decreases in hepatic decompensation events, HCC, and liver-related mortality. In the HALT-C study, patients with advanced fibrosis secondary to HCV infection who achieved an SVR, compared with patients with similarly advanced liver fibrosis who did not achieve an SVR, had a decreased need for liver transplantation (hazard ratio [HR], 0.17, 95% confidence interval [CI], 0.06, 0.46), development of liver-related morbidity and mortality (HR, 0.15, 95% CI, 0.06, 0.38) and HCC (HR, 0.19, 95% CI, 0.04, 0.80). Based on these considerations, the AASLD recommends prompt treatment for individuals with advanced liver disease unless contraindicated (e.g., hypersensitivity) or substantial non-hepatic life-limiting comorbidities are present. Importantly, persons with advanced liver disease also require long-term follow-up and HCC surveillance regardless of treatment outcome.

Post Liver Transplant. In individuals with HCV, infection of the allograft occurs universally in patients in whom viral replication is ongoing at the time of transplantation.[1] Histologic features of hepatitis develop in about 75% of recipients within the first 6 months following liver transplantation. By the fifth postoperative year, if left untreated, up to 30% of patients have progressed to cirrhosis. A small proportion of patients (4% to 7%) develop an accelerated course of liver injury (cholestatic hepatitis C, associated with very high levels of viremia) with subsequent rapid allograft failure. Recurrence of HCV infection post-transplantation has led to shorter period of graft survival for recipients with HCV infection than for recipients who undergo liver transplantation for other indications. Effective antiviral therapy pre-transplantation resulting in a SVR (virologic cure) prevents HCV recurrence post-transplantation. Additionally, complete HCV viral suppression prior to transplantation prevents recurrent HCV infection of the graft in the majority of cases.

Persons with Severe Extrahepatic Manifestations of Chronic HCV Infection. Chronic HCV is associated with a syndrome of cryoglobulinemia and an immune complex and lymphoproliferative disorder that produces arthralgias, fatigue, palpable purpura, renal disease (e.g., membranoproliferative glomerulonephritis), neurologic disease (e.g., peripheral neuropathy, central nervous system vasculitis), and reduced complement levels. Because patients with chronic hepatitis C frequently have laboratory evidence of cryoglobulins (more than 50% in some series), antiviral treatment should be prioritized for those with the syndrome of cryoglobulinemia and symptoms or objective evidence of end-organ manifestations. Although interferon-based regimens can produce clinical remission, the adverse effects of interferon may mimic manifestations of cryoglobulinemia. Although clinical data are not yet available, the use of interferon-free direct-acting antiviral (DAA) regimens is an attractive alternative for these patients.

Glomerular disease results from deposition of HCV-related immune complexes in the glomeruli. Successful treatment of HCV using interferon-based regimens can reverse proteinuria and the nephrotic syndrome, but usually does not fully improve azotemia. No clinical trial data are yet available using interferon-free regimens, but the high rates of SVR using antiviral therapy support their use in management of hepatitis C-related renal disease and cryoglobulinemia.

Elevated HCV Transmission Risk. Persons who have successfully achieved an SVR no longer transmit the virus to others. Therefore, successful treatment benefits public health. Several health models have shown that even modest increases in successful treatment of HCV infection among persons who inject drugs can decrease prevalence and incidence. In addition, mother-to-child transmission of HCV does not occur if the woman is not viremic, providing an additional benefit of curing a woman before she becomes pregnant.

However, the safety and efficacy of treating women who are already pregnant to prevent transmission to the fetus have not yet been established, and thus treatment is not recommended for pregnant women.

In collaboration with recommendations of the Society for Healthcare Epidemiology of America (SHEA), which advises health care workers who have substantial HCV viral replication ($\geq 10^4$ genome equivalents/mL) to be restricted from performing procedures that are prone to exposure, all healthcare workers with confirmed chronic HCV infection should be treated for their HCV. The achievement of SVR in these individuals will not only eliminate the risk of HCV transmission to patients but also decrease the subsequent loss of experienced clinicians. Given concerns about underreporting of infection and transmission, the availability of effective, all-oral regimens should lead to a greater willingness on the part of exposure-prone clinicians to be tested and treated.

Successful treatment of HCV-infected persons at greatest risk for transmission represents an important tool to help stop HCV transmission in those who continue to engage in high-risk behaviors. To guide implementation of hepatitis C treatment as a prevention strategy, studies are needed to define the best candidates for treatment to stop transmission; the additional interventions needed to maximize the benefits of HCV treatment (e.g., preventing reinfection), and the cost effectiveness of the strategies when used in the target populations.

Injection drug use is the most common risk factor for HCV infection in the US and Europe with an HCV seroprevalence from 10% to 70%; injection drug use also accounts for the majority of new infections (approximately 70%) and is the key driving force in perpetuation of the epidemic. Studies of interferon-containing treatments in injection drug users (IDUs) have shown comparable adherence and efficacy rates to patients who do not use injection drugs. A meta-analysis of treatment in active or recent IDUs with peginterferon with or without ribavirin showed SVR rates of 37% and 67% for genotype 1 or 4 and 2 or 3, respectively. Further, the rate of reinfection in this population is lower (2.4/100 person-years of observation) than incident infection in the IDU population in general (6.1-27.2/100 person-years); although reinfection increases with active or ongoing injection drug use (6.44/100 person years) and available data are limited in follow-up duration. Ideally, treatment of HCV-infected persons who inject drugs should be delivered in a multidisciplinary care setting. Regardless of the treatment setting, the AASLD notes that recent and active injection drug use should *not* be seen as an absolute contraindication to HCV therapy. Scale up of HCV treatment in persons who inject drugs is necessary to positively impact the HCV epidemic in the US and globally.

In the past 10 years, there has been an increase in incident HCV infection among human immunodeficiency virus (HIV)-infected men who have sex with men (MSM) who did not report IDU as a risk factor. Recognition and treatment of HCV in this population may represent an important step in preventing subsequent infections. As with persons who inject drugs, HIV-infected MSM with ongoing high-risk sexual practices should be treated for their HCV infection in conjunction with continued education on risk reduction strategies.

The seroprevalence of HCV ranges from 30% to 60% among incarcerated individuals. Treatment of such patients would likely decrease the prevalence of HCV infection in this at-risk population.

The prevalence of HCV infection is elevated in individuals on hemodialysis ranging from 7.8% to 8.9% in the US. The seroprevalence has been found to increase with time on dialysis suggesting that nosocomial transmission, among other risk factors, plays a role in HCV acquisition in these patients. Further HCV infection in such patients has a detrimental impact on kidney transplantation outcomes.

Occupational Exposure. Occupational exposure via skin injury potentially causes up to 16,000 new cases of HCV annually with nurses experiencing the highest exposure rates, followed by medical residents.[12] Fatigue and deviations from infection control practices are contributing factors. Most of these injuries can be prevented by standard precautions, the use of protective gowns and goggles, increased awareness and strict supervision. The average rate of seroconversion after an occupational exposure to HCV-infected blood through accidental needle stick is 1.8%. Guidelines from the AASLD/IDSA/IAS-USA do not support the use of antiviral pre- or post-exposure prophylaxis (Class III, Level C).[1]

Acute HCV. If the decision to treat a patients with acute HCV infection has been made, it is recommended to monitor HCV RNA for at least 12 to 16 weeks to allow for spontaneous clearance prior to starting treatment (Class IIa, Level C).[1] Owing to high efficacy and safety, the same regimens for chronic HCV infection are also recommended for acute infection (Class IIa, Level C).

Limited Life Expectancy. In patients with limited life expectancy for whom HCV therapy would not improve symptoms or prognosis, HCV therapy is not needed.[1] Little evidence exists to support initiation of HCV treatment in patients with limited life expectancy < 12 months due to non-liver related comorbid conditions because such patients are unlikely to realize the benefits of HCV treatment.

Treatment of Chronic HCV

Tables 2 through 14 provide treatment recommendations for treatment-naïve and retreatment patients with chronic HCV, including those with compensated cirrhosis. The Guidelines provide the clinical trial data summaries to support their recommendation: www.hcvguidelines.com. Of note, in patients with mixed genotypes, although rare, when treatment is needed, the choice of antiviral combination and duration should maximize the efficacy against each genotype represented in the assay. Guidelines note data are sparse in this rare situation.

Genotype 1 Chronic HCV

In patients with genotype 1 chronic HCV, several options are recommended in patients with genotypes 1a or 1b. If the genotype subtype cannot be determined, patients should be treated in line with recommendations for genotype 1a.[1] Table 2 below provides recommendations in treatment-naïve and prior relapse patients, Olysio, Sovaldi, and Viekira Pak are all FDA-approved for genotype 1, other recommendations are for off-label use of DAAs. Tables 3 though summarize the recommendations for patients with a previous null or partial response to PR, HCV NS3 protease inhibitor (with PR or with Sovaldi), Sovaldi (with PR or WBR), and NS5A inhibitor (i.e., Daklinza, Harvoni, and Viekira Pak), respectively. Several treatments are not recommended in patients with genotype 1 chronic HCV due to the availability of better-tolerated and/or more effective agents and are cited in the tables below.

Table 2. Genotype 1: Treatment of Chronic HCV in Treatment-Naïve/Relapse Patients.[1]

Genotype	Recommended	FDA Approved (Y/N)	Not Recommended
1a	**Daklinza + Sovaldi** x 12 weeks (no cirrhosis) (Class I, Level B)	N	-**Sovaldi + WBR** x 24 weeks. (Class IIb, Level A) -PR ± Incivek, Victrelis, Sovaldi, or Olysio x 12 to 48 weeks. (Class IIb, Level A)
	Daklinza + Sovaldi ± **WBR** x 24 weeks (cirrhosis) (Class IIa, Level B)	N	
	Harvoni x12 weeks* (Class I, Level A)	**Y**	
	Viekira Pak + WBR x 12 weeks (no cirrhosis) (Class I, Level A)	**Y**	
	Viekira Pak + WBR x 24 weeks (cirrhosis) (Class I, Level A)†	**Y**	
	Sovaldi + Olysio x 12 weeks (no cirrhosis) (Class I, Level A)	Y	
	Sovaldi + Olysio ± WBR x 24 weeks (cirrhosis without Q80K polymorphism) (Class I, Level A)	**Y**	
1b	**Daklinza + Sovaldi** x 12 weeks (no cirrhosis) (Class I, Level B)	N	
	Daklinza + Sovaldi ± **WBR** x 24 weeks (cirrhosis) (Class IIa, Level B)	N	

	Harvoni x12 weeks* (Class I, Level A)	**Y**	-Monotherapy with peginterferon, WBR or DAA. (Class III, Level A)
	Viekira Pak x 12 (Class I, Level A)	**Y** (approved *with* WBR)	
	Sovaldi + Olysio x 12 weeks (no cirrhosis) (Class I, Level A)	**Y**	
	Sovaldi + Olysio ± WBR x 24 weeks (cirrhosis) (Class I, Level A)	**Y**	

Recommendations are listed in alphabetical order by chemical name (not order or preference); HCV – Hepatitis C virus; FDA – Food and Drug Administration; Y – Yes (FDA-approved); N – No (not FDA-approved); WBR – Weight-based ribavirin; PR – Peginterferon/ribavirin; DAA – Direct-acting antiviral; * With Harvoni, *post-hoc* analyses of the two WBR-free arms assessed baseline predictors of relapse and identified lower relapse rates in patients receiving 8 weeks of Harvoni who had HCV RNA levels < 6 million IU/mL at baseline, and was the same for patients with similar baseline HCV RNA levels who received 12 weeks. Shortening treatment to < 12 weeks should be done with caution and performed at the discretion of the practitioner; † In the clinical trial, TURQUOISE-II (enrolled treatment-naïve and treatment-experienced patients with genotype 1a and cirrhosis) overall, SVR12 rates were 89% in the 12-week arm and 95% in the 24-week arm. The difference in SVR12 rate between arms was primarily driven by patients with null response to PR; there was less difference in SVR12 rates in the patients with cirrhosis who were naive to therapy (92% and 95%, respectively).

Table 3. Genotype 1: Treatment of Chronic HCV in Patients who are Prior Non-Responders (Null-Responders or Partial Responders) to PR ONLY.[1]

Genotype	Recommended	FDA-Approved (Y/N)	Not Recommended
1a or 1b	**Daklinza + Sovaldi** x 12 weeks (no cirrhosis) (Class IIa, Level B)	N	-Any regimen containing peginterferon including: Olysio + PR, Sovaldi + PR, Incivek + PR, Victrelis + PR or PR alone. (Class IIb, Level A) -Monotherapy with peginterferon, WBR, or DAA (Class III, Level A) -Any interferon-free regimen containing an HCV protease inhibitor Olysio or paritaprevir (the protease inhibitor in Viekira Pak) [Class IIb, Level A]
	Daklinza + Sovaldi ± **WBR** x 24 weeks (cirrhosis) (Class IIa, Level B)	N	
	Harvoni x 12 weeks (no cirrhosis) (Class I, Level A)	**Y**	
	Harvoni x 24 weeks (cirrhosis) (Class I, Level A)	**Y**	
	Harvoni + WBR x 12 weeks (cirrhosis) (Class I, Level B)	N	
	Viekira Pak + WBR x 12 weeks (genotype 1a, no cirrhosis) (Class I, Level A).	**Y**	
	Viekira Pak + WBR x 24 weeks (genotype 1a) (Class I, Level A)	**Y**	
	Viekira Pak x 12 weeks (genotype 1b with or without cirrhosis) (Class I, Level A)	**Y** (indicated *with* WBR)	
	Sovaldi + **Olysio** x 12 weeks (no cirrhosis) (Class IIa, Level B)	**Y**	
	Sovaldi + Olysio ± WBR x 24 weeks (Class IIa, Level B) (genotype 1a without Q80K polymorphism)	**Y**	

Recommendations are listed in alphabetical order by chemical name (not order or preference); HCV – Hepatitis C virus; FDA – Food and Drug Administration; Y – Yes (FDA-Approved); N – No (not FDA-Approved); PR – Peginterferon and ribavirin; WBR – Weight-based ribavirin; DAA – Direct acting antiviral.

Table 4. Genotype 1: Treatment of Chronic HCV in Patients who are Prior Non-Responders (Null-Responders or Partial Responders) to HCV NS3/4A Protease Inhibitor (with PR or With Sovaldi) [No Prior NS5A].[1]

Genotype	Recommended	FDA-Approved (Y/N)	Not Recommended
1a or 1b	**Daklinza** + **Sovaldi** x 12 weeks (prior HCV protease inhibitor + PR failures, no cirrhosis) (Class I, Level A)	N	Same as not recommended for prior PR failures as described above in Table 3.
	Daklinza + Sovaldi ± WBR x 24 weeks (prior treatment with HCV protease inhibitor + PR, cirrhosis) (Class IIa, Level B)	N	
	Harvoni x 12 weeks (prior HCV protease inhibitor + PR failures, no cirrhosis) (Class I, Level A) Based on limited data, the addition of WBR to this combination is recommended for patients in whom prior treatment with Olysio + Sovaldi has failed (Class I, Level A).	**Y**	
	Harvoni x 24 weeks (prior treatment with HCV protease inhibitor + PR, cirrhosis) (Class I, Level A) Based on limited data, the addition of WBR to this combination is recommended for patients in whom prior treatment with Olysio + Sovaldi has failed (Class I, Level A).	**Y**	
	Harvoni + WBR x 12 weeks (prior treatment with HCV protease inhibitor + PR, cirrhosis) (Class IIa, Level B) Patients with cirrhosis who have previously failed treatment with HCV Olysio + Sovaldi should not be treated with this 12-week regimen.	N	

HCV – Hepatitis C virus; FDA – Food and Drug Administration; Y – Yes (FDA-approved); N – No (not FDA-approved); PR – Peginterferon/ribavirin; WBR – Weight-based ribavirin.

Table 5. Genotype 1: Treatment of Chronic HCV in Patients who are Prior Non-Responders (Null-Responders or Partial Responders) to Sovaldi + PR or Sovaldi + WBR.[1]

Genotype	Recommended	FDA-Approved (Y/N)	Not Recommended
1a or 1b	**Harvoni + WBR** x 12 weeks (no cirrhosis) (Class IIb, Level C)	N*	Same as not recommended for prior PR failures as described above in Table 3.
	Harvoni + WBR x 24 weeks (cirrhosis) (Class IIa, Level C)	N*	

HCV – Hepatitis C virus; FDA – Food and Drug Administration; Y – Yes (FDA-approved); N – No (not FDA-approved); WBR – Weight-based ribavirin; * Harvoni is not FDA-approved in patients previously treated with Sovaldi.

Table 6. Genotype 1: Treatment of Chronic HCV in Patients who are Prior Non-Responders (Null-Responders or Partial Responders) to HCV NS5A inhibitor (Daklinza + Sovaldi, Harvoni, and Viekira Pak).[1]

Genotype	Recommended	FDA-Approved (Y/N)	Not Recommended
1a or 1b	For patients with minimal liver disease, deferral of treatment is recommended. (Class IIb, Level C)	N/A	Same as not recommended for prior PR failures as described above in Table 3.
	For patients with cirrhosis or other patients who require retreatment urgently, testing for resistance-associated variants that confer decreased susceptibility to NS3 protease inhibitors and to NS5A inhibitors is recommended. The specific drugs used in the retreatment regimen should be tailored to the results of this testing. Treatment duration of 24 weeks is recommended and, unless contraindicated, weight-based ribavirin should be added. (Class IIb, Level C) For patients who have NS5A inhibitor RAVs detected and who do not have NS3 inhibitor RAVs detected: Olysio + Sovaldi + ribavirin x 24 (no level of evidence provided). For patients who have both NS3 and NS5A inhibitor RAVs detected, retreatment should be conducted in a clinical trial setting, as an appropriate treatment regimen cannot be recommended at this time.	N	

HCV – Hepatitis C virus; FDA – Food and Drug Administration; Y – Yes (FDA-approved); N – No (not FDA-approved); N/A – Not applicable; PR – Peginterferon/ribavirin; RAVs – Resistance associated variants.

Genotype 2 Chronic HCV

Sovaldi is the only DAA indicated in patients with genotype 2 chronic HCV. Other recommendations are also provided per the AASLD guidelines in Tables 7 and 8 below.

Table 7. Genotype 2: Treatment of Chronic HCV in Treatment-Naïve/Relapse Patients.[1]

Genotype	Recommended	FDA-Approved	Not Recommended
2	**Daklinza + Sovaldi** x 12 weeks (for ribavirin intolerant patients) (Class IIa, Level B)	N	-PR x 24 weeks (Class IIb, Level A) -Monotherapy with peginterferon, WBR, or DAA. Incivek, Victrelis, or ledipasvir (part of Harvoni)-based regimens (all Class III, Level A)
	Sovaldi + WBR x 12 weeks (Class I, Level A)	**Y**	
	Sovaldi + WBR x 16 weeks (cirrhosis) (Class IIb, Level C)	N*	

HCV – Hepatitis C virus; FDA – Food and Drug Administration; Y – Yes (FDA-approved); N – No (not FDA-approved); PR – Peginterferon/ribavirin; WBR – Weight-based ribavirin; DAA – Direct-acting antiviral; * Sovaldi is FDA-approved for 12 weeks with WBR in patients with genotype 2 chronic HCV who are treatment-naïve or who have previously been treated with PR or an NS3A protease inhibitor with PR.

Table 8. Genotype 2: Treatment of Chronic HCV in Patients who are Prior Non-Responders (Null-Responders or Partial Responders).[1]

Genotype	Recommendation	FDA-Approved (Y/N)	Not Recommended
2	***Prior PR treatment***		
	Recommended		
	Sovaldi + WBR x 16 or 24 weeks (Class I, Level A)	N*	- PR ± Incivek or Victrelis (Class IIb, Level A) -Harvoni (Class III, Level A) -Monotherapy with peginterferon, WBR, or DAA (Class III, Level A)
	Alternative		
	Sovaldi + PR x 12 weeks (Class IIa, Level B)	N*	
	Prior Sovaldi + WBR treatment		
	Recommended		
	Daklinza + Sovaldi ± WBR x 24 weeks (interferon-ineligible) (Class IIa, Level C)	N	
	Sovaldi + PR x 12 weeks (interferon eligible) (Class IIa, Level C)	N*	

HCV – Hepatitis C virus; FDA – Food and Drug Administration; Y – Yes (FDA-approved); N – No (not-FDA-approved); * Sovaldi is FDA-approved for 12 weeks with WBR in patients with genotype 2 chronic HCV who are treatment-naïve or who have previously been treated with PR or an NS3A protease inhibitor with PR; WBR – Weight-based ribavirin.

Genotype 3 Chronic HCV

There are two DAAs indicated for the treatment of patients with genotype 3 chronic HCV, Daklinza and Sovaldi. Tables 9 and 10 provide the recommended and alternative regimens for patients with genotype 3 chronic HCV.

Table 9. Genotype 3: Treatment of Chronic HCV in Treatment-Naïve/Relapse Patients.[1]

Genotype	Recommendation	FDA-Approved (Y/N)	Not Recommended
3	**Recommended**		
	Daklinza + Sovaldi x 12 weeks (no cirrhosis) (Class I, Level A)	**Y**	-PR x 24 or 48 weeks (Class IIb, Level A) -Monotherapy with peginterferon, WBR, or DAA (Class III, Level A) -Incivek, Victrelis, or Olysio-based regimens (Class III, Level A)
	Daklinza + Sovaldi ± WBR x 24 weeks (cirrhosis) (Class IIa, Level C)	N	
	Sovaldi + **PR** x 12 weeks (for interferon-eligible patients) (Class I, Level A)	N	
	Alternative		
	Sovaldi + **WBR** x 24 weeks (interferon ineligible) (Class I, Level A)	N	

HCV – Hepatitis C virus; FDA – Food and Drugs Administration; Y – Yes (FDA-approved); N – No (not FDA-approved); PR – Peginterferon/ribavirin; WBR – Weight-based ribavirin; DAA – Direct-acting antiviral.

Table 10. Genotype 3: Treatment of Chronic HCV in Patients who are Prior Non-Responders (Null-Responders or Partial Responders).[1]

Genotype	Recommended	FDA-Approved (Y/N)	Not Recommended
3	***Prior PR treatment***		
	Daklinza + Sovaldi x 12 weeks (no cirrhosis) (Class I, Level A)	**Y**	-PR x 24 or 48 weeks (Class IIb, Level A) -Incivek-, Victrelis-, Olysio-based regimens (Class III, Level A) -Monotherapy with peginterferon, WBR, DAA (Class III, Level A)
	Daklinza + Sovaldi + WBR x 24 weeks (interferon ineligible and cirrhosis) (Class IIa, Level C)	N*	
	Sovaldi + PR x 12 weeks (no cirrhosis) (Class I, Level A) [Interferon-eligible]	**Y**	
	Prior Sovaldi + WBR treatment		
	Daklinza + Sovaldi + WBR x 24 weeks (Class IIa, Level C)	N*	
	Sovaldi + PR x 12 weeks (Class IIa, Level C)	**Y**	

HCV – Hepatitis C virus; FDA – Food and Drug Administration; Y – Yes (FDA-approved); N – No (not FDA-approved); PR – Peginterferon/ribavirin; WBR – Weight-based ribavirin; DAA – Direct-acting antiviral; * Daklinza is indicated in combination with Sovaldi for 12 weeks.

Genotype 4 Chronic HCV

Two DAAs are indicated for patients with genotype 4 chronic HCV; Sovaldi and Technivie. Additional recommendations from AASLD are provided below in Tables 11 and 12.

Table 11. Genotype 4: Treatment of Chronic HCV in Treatment-Naïve/Relapse Patients.[1]

Genotype	Recommendation	FDA-Approved (Y/N)	Not Recommended
4	**Recommended**		
	Harvoni x 12 weeks (Class IIb, Level B)	N	-PR ± Olysio x 24 to 48 weeks (Class IIb, Level A) -Monotherapy with peginterferon, WBR, or DAA. Incivek or Victrelis-based regimens (all Class III, Level A).
	Technivie + WBR x 12 weeks (Class I, Level B)	**Y**	
	Sovaldi + **WBR** x 24 weeks (Class IIa, Level B)	N*	
	Alternative		
	Sovaldi + PR x 12 weeks (Class II, Level B)	**Y**	

HCV – Hepatitis C virus; FDA – Food and Drug Administration; Y – Yes (FDA-approved); N – No (not FDA-approved); PR – Peginterferon/ribavirin; WBR – Weight-based ribavirin; DAA – Direct-acting antiviral; * Sovaldi is indicated in combination with PR for 12 weeks in patients with genotype 4 chronic HCV.

Table 12. Genotype 4: Treatment of Chronic HCV in Patients who are Prior Non-Responders (Null-Responders or Partial Responders) to <u>PR ONLY</u> Without Decompensated Cirrhosis.[1]

Genotype	Recommended	FDA-Approved (Y/N)	Not Recommended
4	**Harvoni** x 12 weeks (Class IIa, Level B)	N	-PR ± Incivek or Victrelis (Class IIb, Level A) -Monotherapy with peginterferon, WBR, or DAA (Class III, Level A)
	Technivie + WBR x 12 weeks (Class IIa, Level B)	**Y**	
	Sovaldi + PR x 12 weeks (Class IIa, Level B)	**Y**	
	Sovaldi + WBR x 24 weeks (Class IIa, Level B)	N	

HCV – Hepatitis C virus; PR – Peginterferon/ribavirin; FDA – Food and Drug Administration; Y – Yes (FDA-approved); N – No (not FDA-approved); WBR – Weight-based ribavirin; DAA – Direct-acting antiviral/

Genotype 5/6 Chronic HCV

Very limited data exist in patients with genotypes 5 and 6 chronic HCV and none of the DAAs are currently approved in this genotype. Nonetheless, the AASLD provides recommendations based on the available information.

Table 13. Genotype 5/6: Treatment of Chronic HCV in Treatment-Naïve/Relapse Patients.[1]

Genotype	Recommendation	FDA-Approved (Y/N)	Not Recommended
5 and 6 [α]	**Recommended**		
	Harvoni x 12 weeks (Class IIa, Level B)	N	-Monotherapy with peginterferon, WBR, or DAA (Class III, Level A) -Incivek or Victrelis-based regimens (Class III, Level A)
	Alternative		
	Sovaldi + PR x 12 weeks (Class IIa, Level B)	N	

HCV – Hepatitis C virus; FDA – Food and Drug Administration; Y – Yes (FDA-approved); N – No (not FDA-approved); [α] Few data are available to help guide decision making in patients infected with genotype 5 or 6 chronic HCV, nonetheless, for patients for whom immediate treatment is required the recommendations in the table have been drawn from available data; WBR – Weight-based ribavirin; DAA – Direct-acting antiviral; PR – Peginterferon/ribavirin.

Table 14. Genotype 5/6: Treatment of Chronic HCV in Patients who are Prior Non-Responders (Null-Responders or Partial Responders)[†].[1]

Genotype	Recommendation	FDA-Approved (Y/N)	Not Recommended
5 and 6[α]	**Recommended**		
	Harvoni x 12 weeks (Class IIa, Level C)	N	-Incivek- or Victrelis-containing regimens (Class III, Level A) -Monotherapy with peginterferon, WBR, or DAA (Class III, Level A)
	Alternative		
	Sovaldi + PR x 12 weeks (Class IIa, Level C)	N	

HCV – Hepatitis C virus; [†] Prior treatment history not specified; [α] Few data are available to help guide decision making in patients infected with genotype 5 or 6 chronic HCV; nonetheless, for patients for whom immediate treatment is required the recommendations in the table have been drawn from available data; FDA – Food and Drug Administration; Y – Yes (FDA-approved); N – No (not FDA-approved); WBR – Weight-based ribavirin; DAA – Direct-acting antiviral; PR – Peginterferon/ribavirin.

Treatment of HCV in Unique Patient Populations

The guidelines identify several unique patient populations where distinct recommendations are made.

Chronic HCV and Decompensated Cirrhosis (Child Pugh Class B or C)

Patients with decompensated cirrhosis and HCV post liver transplant also represent a unique patient population that must be carefully treated do to the state of their disease. None of the DAAs are FDA-indicated in patients with decompensated cirrhosis. Sovaldi is indicated in patients with HCC awaiting liver transplant, but not transplant due to other causes. Recommendations are based on literature with the respective agents. The guidelines note that in all cases patients should be referred to a medical practitioner with expertise in the condition (ideally a liver transplant center) [Class I, Level C]. The recommended

regimens are for patients who may or may not be candidates for liver transplantation, including those with HCC.

Table 15. Genotype 1 or 4: Treatment of Patients with Chronic HCV and Decompensated Cirrhosis.[1]

Genotype	Recommended	Not Recommended
1 or 4	**Daklinza + Sovaldi + ribavirin** (600 mg increased as tolerated) x 12 weeks (Class II, Level A)	-Any interferon-based therapy (Class III, Level A) -Monotherapy with peginterferon, ribavirin, or DAA (Class III, Level A) -Incivek-, Victrelis-, or Olysio-based regimens, or Viekira Pak (Class III, Level A)
	Harvoni + ribavirin (600 mg increased as tolerated) x 12 weeks (Class IIb, Level C)	
	Ribavirin Intolerant or Ineligible: **Daklinza + Sovaldi** x 24 weeks (Class IIb, Level A)	
	Prior Sovaldi-Based Treatment Failures: **Harvoni + ribavirin** (600 mg increased as tolerated) x 24 weeks (Class IIb, Level C)	

HCV – Hepatitis C virus; DAA – Direct acting antiviral.

Table 16. Genotype 2 or 3: Treatment of Patients with Chronic HCV and Decompensated Cirrhosis.[1]

Genotype	Recommended	Not Recommended
2 or 3	**Daklinza + Sovaldi + ribavirin (**600 mg increased as tolerated) x 12 weeks (Class II, Level A)	-Any interferon-based therapy (Class III, Level A) -Monotherapy with peginterferon, ribavirin, or DAA (Class III, Level A) -Incivek-, Victrelis-, or Olysio-based regimens, or Viekira Pak (Class III, Level A)
	Sovaldi + WBR (with consideration of hemoglobin and creatinine clearance) for up to 48 weeks(Class IIb, Level B)	

HCV – Hepatitis C virus; WBR – Weight-based ribavirin; DAA – Direct acting antiviral; N/A – Not applicable.

Recurrent HCV Post Liver Transplantation

Viekira Pak is the only DAA specifically indicated in the post-liver transplant setting. Other recommendations from AASLD are based on clinical trial data.

Table 17. Genotype 1 or 4: Treatment of Patients with Recurrent HCV After Liver Transplant.[1]

Genotype	Prior Treatment History	Recommendation	Not Recommended
1 or 4	***Recurrent HCV After Liver Transplantation (Including Compensated Cirrhosis)***		
	Recommended		
	Treatment-naïve or experienced	**Daklinza + Sovaldi + ribavirin** (600 mg increased as tolerated) x 12 weeks (Class I, Level B)	-Regimens containing peginterferon, monotherapy with peginterferon, WBR, or DAA -Incivek or Victrelis-based regimens (all Class III, Level A)
		Harvoni + WBR x 12 weeks (Class I, Level B)	
	Treatment-naïve ribavirin intolerant or ineligible	**Daklinza + Sovaldi** x 24 weeks (Class IIb, Level C)	
		Harvoni x 24 weeks (Class I, Level B)	
	Alternative		
	Treatment-naïve or experienced	Genotype 1: **Sovaldi + Olysio ± WBR** x 12 weeks (Class I, Level B)	
		Genotype 1 and Metavir F0 to F2 (no cirrhosis): **Viekira Pak + WBR** x 24 weeks (Class I, Level B)	
	Recurrent HCV Post Liver Transplantation (Decompensated Cirrhosis)		
	Recommended		
	Treatment-naïve or experienced	**Harvoni + ribavirin** (600 mg increased as tolerated) x 12 weeks (Class I, Level B)	-Regimens containing peginterferon -Regimens containing Olysio -**Viekira Pak** -Monotherapy with peginterferon, WBR, or DAA -Incivek- or Victrelis-based regimens (all Class III, Level A)

HCV – Hepatitis C virus; WBR – Weight-based ribavirin; DAA – Direct-acting antiviral; WBR – Weight-based ribavirin.

Table 18. Genotype 2: Treatment of Patients with Recurrent HCV After Liver Transplant.[1]

Genotype	Prior Treatment History	Recommended	Not Recommended
2	***Recurrent HCV After Liver Transplantation (Including Compensated Cirrhosis)***		
	Treatment-naïve or experienced	**Daklinza + Sovaldi + ribavirin** (600 mg increased as tolerated) x 12 weeks (Class II, Level A)	-Regimens containing peginterferon, monotherapy with peginterferon, WBR, or DAA -Incivek or Victrelis-based regimens (all Class III, Level A)
		Sovaldi + WBR x 24 weeks (Class IIb, Level C)	
		Ribavirin Intolerant/Ineligible: **Daklinza + Sovaldi** x 24 weeks (Class IIb, Level C)	

Table 18 (continued). Genotype 2: Treatment of Patients with Recurrent HCV After Liver Transplant.[1]

Genotype	Prior Treatment History	Recommended	Not Recommended
2	***Recurrent HCV Post Liver Transplantation (Decompensated Cirrhosis)***		
	Treatment-naïve or experienced	**Sovaldi + ribavirin** (600 mg increased as tolerated) x 24 weeks (Class IIb, Level C)	-Regimens containing peginterferon -Regimens containing Olysio -**Viekira Pak** -Monotherapy with peginterferon, WBR, or DAA. Incivek- or Victrelis-based regimens (all Class III, Level A)

HCV – Hepatitis C virus; WBR – Weight-based ribavirin; DAA – Direct-acting antiviral.

Table 19. Genotype 3: Treatment of Patients with Recurrent HCV After Liver Transplant.[1]

Genotype	Prior Treatment History	Recommended	Not Recommended
3	***Recurrent HCV After Liver Transplantation (Including Compensated Cirrhosis)***		
	Treatment-naïve or experienced	**Daklinza + Sovaldi + ribavirin** (600 mg increased as tolerated) x 12 weeks (Class II, Level A)	-Regimens containing peginterferon, monotherapy with peginterferon, WBR, or DAA -Incivek or Victrelis-based regimens (all Class III, Level A)
		Sovaldi + WBR x 24 weeks (Class I, Level B)	
	Treatment-Naïve and Ribavirin Intolerant/ Ineligible	**Daklinza + Sovaldi** x 24 weeks (Class IIb, Level C)	
	Recurrent HCV Post Liver Transplantation (Decompensated Cirrhosis)		
	Treatment-naïve or experienced	**Sovaldi + ribavirin** (600 mg increased as tolerated) x 24 weeks (Class I, Level B)	-Regimens containing peginterferon -Regimens containing Olysio -**Viekira Pak** -Monotherapy with peginterferon, WBR, or DAA -Incivek- or Victrelis-based regimens (all Class III, Level A)

HCV – Hepatitis C virus; WBR – Weight-based ribavirin; DAA – Direct-acting antiviral.

Renal Impairment

For patients with renal impairment, dose reductions with peginterferon and ribavirin are recommended depending on the degree of renal impairment (see Table 21). There are limited data with the DAAs. For patients with mild to moderate renal impairment (CrCl 30 mL/min to 80 mL/min), no dose adjustment is required when using Sovaldi, Olysio, Harvoni, or Viekira Pak (Class I, Level A). **For patients with CrCl < 30 mL/min who do not have cirrhosis and in whom the urgency to treat is high and renal transplant is not an immediate option, Viekira Pak can be considered to treat or retreat HCV infection in**

patients with appropriate genotypes. However, this is based on limited data on safety and efficacy. Caution is recommended when considering the use of ribavirin in patients with genotype 1a HCV, owing to the potential for hemolysis in this population and should be restricted to those with a baseline hemoglobin concentration > 10 mg/dL. The recommended ribavirin dose is 200 mg three times per week to daily, with discontinuation if hemoglobin level declines by more than 2 g/dL despite the use of erythropoietin (Class IIb, Level B). **For patients with CrCl < 30 mL/min, treatment with Sovaldi-containing regimens can be considered after consultation with an expert, because safety and efficacy data are not available in these patients** (Class IIb, Level C). Additional recommendations for patients with renal impairment are addressed in Table 20 below.

Table 20. Recommended Regimens for Patients with CrCl < 30 mL/min Without Cirrhosis but for Whom Urgency to Treat or Retreat is High and Renal Transplant is Not an Immediate Option*.

Genotype	Recommended	FDA Approved (Y/N)
Genotype 1a	**Viekira Pak + ribavirin** (reduced dose, 200 mg three times weekly to daily); use ribavirin only in patients with baseline hemoglobin > 10 g/dL	**Y** (indicated with WBR)
Genotype 1b	**Viekira Pak** (Class IIb, Level B)	**Y**
Genotype 4	**Technivie** (Class IIb, Level B)	**Y** (indicated with WBR)
Genotypes 2, 3, 5, and 6	**Pegylated interferon + dose-adjusted ribavirin** if treatment is needed.	**Y**

CrCl – Creatinine clearance; * For patients with CrCl < 30 mL/min who do not have cirrhosis but for whom the urgency to treat (or retreat) is high, consultation with an expert is recommended, to assess the appropriateness of a Sovaldi-containing regimen, because safety and efficacy data are not available in this setting (Class IIb, Level C); WBR – Weight-based ribavirin.

Table 21. Dose Adjustments Needed for Patients with Renal Impairment (Prescribing Information).[3-10]

Renal impairment (CrCl)	Daklinza	Harvoni	Olysio	Pegylated Interferon	Ribavirin	Sovaldi	Technivie	Viekira Pak
Mild (50 to 80 mL/min)	N	N	N	N	N	N	N	N
Moderate (30 to 50 mL/min)	N	N	N	Dose reduction	Dose reduction	N	N	N
Severe (< 30 mL/min)	N	No recommendation (higher exposure)	N	Dose reduction	Dose reduction	Not established	N	N
ESRD with HD	N	No recommendation (higher exposure)	Not studied	Dose reduction	Dose reduction	Not established	Not studied	Not studied

CrCl – Creatinine clearance; N – No dose adjustment needed; ESRD – End-stage renal disease; HD – Hemodialysis.

Daklinza is 99% plasma bound and primarily metabolized by the liver and excreted in feces, and less than 10% of Daklinza is excreted by the kidneys.[1] The pharmacokinetics and safety of a single dose of Daklinza in patients who did not have HCV infection, with or without impaired renal function were assessed. Patients with ESRD on HD (eGFR < 15 mL/min/1.73m^2) were matched by age, sex, and weight to healthy controls (CrCl < 90 mL/min). Patients with moderate and severe renal impairment were also included in the study

in which all patients received a single dose of Daklinza 60 mg. Neither Daklinza maximum concentration (C_{max}) nor plasma bound fraction changed substantially in patients with moderate or severe renal impairment and ESRD, compared with healthy control patients. A single dose of Daklinza was generally well tolerated by patients with renal impairment. Daklinza can be administered to patients with renal impairment, including ESRD, without dose modification.

The HCV-TARGET study is an ongoing prospective, observational cohort study evaluating the use of DAAs across clinical practices in North American and Europe.[1] The study reported the safety and efficacy of sofosbuvir-containing regimens in patients with mild to severe renal dysfunction (eGFRs < 30, 31-45, 40-60, and > 60 mL/min). Patients received different regimens that included Sovaldi (pegylated interferon + ribavirin, and Sovaldi; Olysio + Sovaldi ± ribavirin; or Sovaldi + ribavirin). Overall the regimens were well tolerated with no increased discontinuation among patients with lower eGFRs. The rates of SVR12 were similar across the groups regardless of renal function. Notably, there were progressive deterioration of renal function and renal symptoms in patients with eGFRs < 30 mL/min/1.73 m^3., suggesting the need for close monitoring of these patients. Patients with low baseline renal function had a higher frequency of anemia, worsening renal dysfunction, and more severe AEs, but treatment responses remain high and comparable to those without renal impairment.

Data on patients treated with a regimen of Olysio + low-dose Sovaldi without ribavirin have been reported. In one study, 18 HCV-infected patients (11 requiring hemodialysis, 3 with a mean eGFR of 16 mL/min) underwent open-label treatment with Olysio and Sovadli, all patients received full-dose Olysio (150 mg) daily.[1] The Sovaldi dose was reduced to 200 mg daily in 15 patients and 400 mg every other day in 3 patients. The length of therapy was 12 weeks in 17 patients and 24 weeks in 1 patient with cirrhosis. One patient developed new onset hepatic encephalopathy and another developed uncontrolled diarrhea, both requiring hospitalizations during treatment. Minor AEs were fatigue (28%), anemia (11%), rash or itching (11%), and nausea (5%) and were managed medically; there were no treatment discontinuations. Of the 16 patients who completed treatment, only 9 patients reached relevant milestones. Per the current per-protocol analysis, SVR4 was seen in 91% of patients and SVR12 in 89% of patients. One patient with cirrhosis (who had a prior HCV protease inhibitor-containing treatment failure) relapsed within 4 weeks after completion of treatment. In summary, the regimen of Olysio and reduced-dose Sovaldi is safe and well tolerated. In another study, 12 patients with eGFRs < 30 mL/min received Sovaldi (400 mg) and Olysio (150 mg). The regimen was well tolerated and resulted in viral suppression in all patients.

Single-dose pharmacokinetics of the fixed-dose combination of Viekira Pak was evaluated in HCV-seronegative volunteers with mild (eGFR 60 to 89 mL/min), moderate (eGFR 30 to 59 mL/min), or severe (eGFR <30 mL/min) renal impairment.[1] The results concluded changes in pharmacokinetics that were not considered to be clinically relevant in HCV-infected patients.

Twenty patients with HCV genotype 1 infection and stage 4 or 5 (eGFR < 30 mL/min) chronic kidney disease (CKD) without cirrhosis were treated with Viekira Pak with or without ribavirin in a multicenter, open-label Phase IIb study.[1] Notably, 65% had CKD requiring hemodialysis. Ribavirin (in those with HCV genotype 1a only) was dosed 4 hours before hemodialysis and monitored with weekly hemoglobin assessments. RBV doses were suspended for ≥ 2 g/dL or more drop in hemoglobin level and resumed when the hemoglobin level normalized. All patients (n = 10/10) achieved SVR4. Interestingly, the use of ribavirin was associated with more of a drop in hemoglobin level, and 8 of 13 patients required interruption of ribavirin dosing. Among these eight patients, four also required erythropoietin treatment during the first 7 weeks of therapy. Mean drug concentrations (C_{trough}) of all drugs were measured and levels were within the range that was observed with previous pharmacokinetic studies in healthy volunteers. In summary, most patients with HCV genotype 1 with or without cirrhosis who were treated with Viekira Pak with or

without ribavirin achieved viral suppression. However, ribavirin–induced anemia can occur frequently, and close monitoring of all patients and judicious dose reductions of ribavirin are required.

Sovladi/sofosbuvir enters the hepatocyte where it is metabolized to its active form, GS-461203.[1] The downstream inactive nucleoside metabolite GS-331007 is almost exclusively eliminated from the body renally, mediated through a combination of glomerular filtration and active tubular secretion. Results of Phase II and Phase III clinical trials of sofosbuvir-containing regimens excluded patients with serum creatinine (SCr) levels > 2.5 mg/dL or CrCl levels < 60 mL/min. The pharmacokinetics of a single 400 mg dose of sofosbuvir were assessed in persons not infected with HCV (study P7977-0915) who had mild (eGFR >50 mL/min/1.73 m2 and <80 mL/min/1.73 m2), moderate (eGFR >30 mL/min/1.73 m2 and <50 mL/min/1.73 m2), or severe (eGFR <30 mL/min/1.73 m2) renal impairment and persons with ESRD who required hemodialysis. Compared with persons with normal renal function (eGFR >80 mL/min/1.73 m2), the sofosbuvir area under the curve (AUC; 0-inf) increased by 61%, 107%, and 171% in patients with mild, moderate, and severe renal impairment, respectively; GS-331007 AUC ($_{0\text{-inf}}$) increased by 55%, 88%, and 451%, respectively. In subjects with ESRD, sofosbuvir and GS-331007 AUC ($_{0\text{-inf}}$) increased by 28% and 1280%, respectively, when sofosbuvir was dosed 1 hour before hemodialysis. Sofosbuvir and GS-331007 AUC ($_{0\text{-inf}}$) increased by 60% and 2070%, respectively, when sofosbuvir was dosed 1 hour after hemodialysis. No dosage adjustment is required for patients with mild or moderate renal impairment (CrCl 30 mL/min-80 mL/min). The safety of sofosbuvir has not been established in patients with severe renal impairment or ESRD. Therefore, a dose recommendation cannot be provided for these populations at this time, although a dedicated study to evaluate optimal dosing of sofosbuvir in HCV-infected patients with severe renal impairment or ESRD on hemodialysis is currently underway.

No clinically relevant changes in ledipasvir pharmacokinetics were found in subjects with normal renal function and those with severe renal impairment (eGFR <30 mL/min) after a single dose of 90 mg of ledipasvir was administered.[1]

HIV Co-Infection

In patients with HIV co-infection, in general, treatment recommendations are the same as recommended for non-co-infected patients (as described above in tables 2 through 14); however, some special recommendations apply. With the availability of HCV DAAs, patients with HIV and HCV co-infection are achieving rates of SVR12 similar to that of non-co-infected individuals. However, treatment of patients with HIV co-infection requires continued awareness and attention to the complex drug interactions that can occur between DAAs and ART. Table 22 below provides some recommendations in the treatment of patients with HIV and HCV co-infection. HIV/HCV co-infected individuals should be treated and retreated the same as individuals without HIV infection, after recognizing and managing interactions with ARVs (Class I, Level B). Although most treatment recommendations for patients co-infected with HIV are the same as for non-coinfected patients, **use of regimens < 12 weeks is not recommended in patients with HIV co-infection (Class IIb, Level C).** Daklinza + Sovaldi ± WBR as is recommended in patients without HIV is recommended when ARV regimen changes cannot be made to accommodate alternative HIV DAAs (Class I, Level B)

Table 22. AASLD General Recommendations for the Treatment of Patients with HIV and HCV Co-Infection.

DAA	Recommendations
Daklinza	Requires dose adjustment with ritonaivr-boosted atazanavir (Daklinza 30 mg) and efavirenz or nevirapine (Daklinza 90 mg) (Class IIa, Level B)
Harvoni	Use with any tenofovir disoproxil fumarate-containing product mandates consideration of CrCl rate and should be avoided in patients with CrCl < 60 mL/minute. Because potentiation of this effect occurs when tenofovir disoproxil fumarate-(or containing product) is used in combination with ritonavir-boosted HIV protease inhibitors, ledipasvir (part of Harvoni) should be avoided with this combination unless the ART cannot be changed and the urgency of treatment is high. (Class IIa, Level C)
	Do not use with cobicistat when given with tenofovir disoproxil fumarate (Class III, Level C)
	Do not use with tipranavir (Class III, Level B)
Viekira Pak	Can be used with ARVs with which it does not have substantial interactions: atazanavir, dolutegravir, emtricitabine, enfuvirtide, lamivudine, raltegravir, tenofovir disoproxil fumarate. The dose of ritonavir used for boosting HIV protease inhibitors may need to be adjusted or held when administered with Viekira Pak, then restored when HCV treatment is completed. The HIV protease inhibitor should be administered at the same time as the fixed-dose combination. (Class IIa, Level C)
	Do not use with darunavir, efavirenz, ritonavir-boosted lopinavir, or rilpivirine. (Class III, Level B)
	Do not use in patients who are not taking ARV therapy for HIV. (Class III, Level B)
Olysio	Should be used with ARVs with which it does not have clinically significant interactions: abacavir, emtricitabine, enfuvirtide, lamivudine, maraviroc, raltegravir, (and probably dolutegravir), rilpivirine, tenofovir disoproxil fumarate. (Class IIa, Level B)
	Do not use with cobicistat, efavirenz, etravirine, nevirapine, or any HIV protease inhibitor (Class III, Level B)
Ribavirin	**Do not use with didanosine, stavudine, or zidovudine** (Class III, Level B)

AASLD – American Association for the Study of Liver Diseases; HIV – Human immunodeficiency; HCV – Hepatitis C virus; DAA – Direct-acting antivirals; CrCl – Creatinine clearance; ART – Antiretroviral therapy; ARV – Antiretroviral.

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PRIOR AUTHORIZATION POLICY

POLICY: Hepatology – Givlaari™ (givosiran injection solution, for subcutaneous use – Alnylam Pharmaceuticals)

DATE REVIEWED: 12/18/2019; selected revision 05/20/2020

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. 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. The recommended dose is 2.5 mg/kg administered by subcutaneous injection once monthly by a healthcare professional only.

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 cell, resulting in oxygen depletion. AHPs are a subgroup of porphyrias in which the enzyme deficiency occurs within the liver. 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] Symptoms and treatments for AIP, VP, ALAD, and HCP are similar. Unlike AIP and ADP patients, 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.

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

78. Acute Hepatic Porphyria. 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) 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

C) Givlaari is prescribed by, or in consultation with, with a gastroenterologist, hepatologist, or a physician who specializes in acute hepatic porphyria.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Givlaari 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. 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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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

46. 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:

126. 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.

127. 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]

128. 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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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

26. 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.

27. **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:

129. 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.

130. 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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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 against angioedema attacks in adolescent and adult patients with HAE.

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:

131. **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.

132. 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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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:

133. Hereditary Angioedema (HAE) Prophylaxis. Data are not available and icatibant is not indicated for prophylaxis of HAE attacks.

134. 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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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:

3. **Hereditary Angioedema (HAE) Prophylaxis.** Data are not available and Kalbitor is not indicated for the prophylaxis of HAE attacks.

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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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):
   - **E)** 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.
   - **F)** 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:

135. **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.

136. 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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PRIOR AUTHORIZATION POLICY

POLICY: Hetlioz™ (tasimelteon capsules – Vanda Pharmaceuticals)

DATE REVIEWED: 04/15/2020

OVERVIEW

Hetlioz, a melatonin receptor agonist, is indicated for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24).[1] 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] The recommended dosage of Hetlioz is 20 mg once daily (QD) taken before bedtime at the same time every night.[1] Take Hetlioz without food. The most common adverse events (AEs) with Hetlioz include headache (17%), alanine aminotranferase increases (10%), and nightmares or abnormal dreams (10%). Hetlioz has a Warning and Precaution regarding somnolence and that it can potentially impair performance if doing activities that require complete mental alertness.[1]

Clinical Efficacy

The efficacy of Hetlioz was established in two, Phase III, randomized, placebo-controlled, double-masked, multicenter trials pivotal studies involving totally blind patients who reported no light perception with Non-24. SET (Safety and Efficacy of Tesimelteon) [n = 84] evaluated Hetlioz for up to 6 months and RESET (Randomized withdrawal study of the Safety and Efficacy of Tasimelteon) evaluated the effects of Hetlioz

withdrawal.[1-2] Patients in SET were aged 18 to 75 years 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. Upon completion of SET, patients were offered continued participation in RESET.[2] In SET, patient diaries were used for an average of 88 days during screening and 133 days during randomization.[1-2] 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] The patient's circadian rhythm is calculated by various measures, the most common of which includes assessing a melatonin metabolite in the urine.[3-5] The step down endpoint of the clinical response rate demonstrated that 24% of patients given Hetlioz (n = 9/38) became entrained an reached an Non-24 Clinical Response Scale (N24CRS) score ≥ 3 compared with none of the patient given placebo (P = 0.0028).[2] 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] The RESET trial (n = 20) involved patients who received Hetlioz for 12 weeks and became entrained.[1-3] 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]

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).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Hetlioz. Because of the specialized skills required for evaluation and diagnosis of patients treated with Hetlioz in Non-24, approval requires Hetlioz to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 12 months in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

Food and Drug Administration (FDA)-Approved Indications

1. **Non-24-Hour Sleep Wake Disorder (Non-24), Initial Therapy.** Approve for 6 months 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 totally blind with no perception of light; AND

C) The medication is prescribed by, or in consultation with, a physician who specializes in the treatment of sleep disorders; AND
D) The diagnosis of Non-24 is confirmed by meeting ONE of the following conditions (i or ii):
  i. Assessment of at least one physiologic circadian phase marker (e.g., measurement of urinary melatonin levels, dim light melatonin onset [as measured in blood or saliva], assessment of core body temperature); OR
  ii. 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
E) The patient meets both of the conditions below (i and ii):
  i. The 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
  ii. The patient did not achieve adequate results with melatonin therapy according to the prescribing physician (e.g., entrainment, clinically meaningful or significant increases in nighttime sleep, clinically meaningful or significant decreases in daytime sleep).

2. Non-24-Hour Sleep Wake Disorder (Non-24), Continuation Therapy. Approve for 12 months 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 totally blind with no perception of light; AND
C) The medication is prescribed by, or in consultation with, a physician who specializes in the treatment of sleep disorders; AND
D) The 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 (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]); AND
E) The patient has achieved adequate results with Hetlioz therapy according to the prescribing physician (e.g., entrainment, clinically meaningful or significant increases in nighttime sleep, clinically meaningful or significant decreases in daytime sleep).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Hetlioz 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.)

137. 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.

138. 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 AEs 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.

139. **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 not 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]

140. **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.

141. 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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PRIOR AUTHORIZATION POLICY

POLICY: Homozygous Familial Hypercholesterolemia – Juxtapid® (lomitapide capsules – Aegerion Pharmaceuticals)

REVIEW DATE: 10/09/2019

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, 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 has not been determined.

Repatha® (evolocumab injection for subcutaneous [SC] use) 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.[5] The recommended dose is 420 mg SC once monthly (QM). In patients with HoFH with a baseline LDL-C of 349 mg/dL, the difference between Repatha and placebo in the mean percent LDL-C from baseline in a 12-week study was -31%. 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.[5] Simvastatin, atorvastatin, and rosuvastatin are indicated for the management of patients with HoFH.[6-8] Ezetimibe is also indicated for use in combination with atorvastatin or simvastatin in patients with HoFH.[9] Ezetimibe/simvastatin tablets are indicated for use in HoFH.

Clinical Data

The efficacy of Juxtapid as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, were assessed in a multinational, single-arm, Phase III, open-label, 78-week pivotal trial that involved adults with HoFH (n = 29).[1,2] A 6-week run-in period was performed to stabilize lipid modifying therapies which included the establishment of an LDL apheresis schedule if applicable. Patients initiated therapy with Juxtapid 5 mg QD for 2 weeks, and then escalated the dose to 10, 20, 40, and 60 mg QD at Weeks 2, 6, 10, and 14, respectively, until an individually determined maximum dose was established based on safety and tolerability. Patients remained at their maximum dose to the end of the 26-week efficacy phase. For an additional 52 weeks, patients were maintained on Juxtapid therapy (i.e., dose not increased above the maximum tolerated dose) to evaluate long-term safety (Weeks 26 through Week 78) and at that time concomitant lipid modifying therapies, including LDL apheresis, could be changed according to the investigator.[2] The diagnosis of HoFH was defined by the presence of at least one of the following clinical criteria: 1) documented functional mutation(s) in both low-density lipoprotein receptor (LDLR) alleles or alleles know to impact LDL receptor functionality; or 2) skin fibroblast LDL-receptor activity < 20% normal; or 3) untreated total-C > 500 mg/dL and triglyceride (TG) < 300 mg/dL and both parents with documented untreated total-C > 250 mg/dL.[1] The primary efficacy endpoint was the percent change from baseline in LDL-C after 26 weeks of therapy. Other lipid parameters were also assessed. The mean patient age was 30.7 years (range, 18 to 55 years), 16 patients (55%) were men, and most of the patients (86%) were Caucasian.[1-2] All 29 patients were either homozygotes or compound heterozygotes for mutations in the *LDLR* gene or genes impacting LDL-receptor functionality.[2] Concomitant lipid modifying treatments at baseline included one or more of the following: statins (93%), ezetimibe (Zetia®, generics) [76%], nicotinic acid (10%), bile acid sequestrants (3%), and fibrates (3%).[1,2] The main statins used were rosuvastatin tablets and atorvastatin.[2] Apheresis was used as a therapy in 18 patients (62%) and the frequency ranged from weekly to every 6 weeks.[2] ***Results.*** In total, 79% of patients (n = 23/29) completed the efficacy endpoint at Week 26, as well as the 78-week treatment period.[1,2] AEs led to premature discontinuation for five patients.[1] At Week 26, the mean and median percent changes in LDL-C from

baseline were -40% (P < 0.001) and -50%, respectively, based on the intent-to-treat (ITT) population with last observation carried forward (LOCF) for those who discontinued the trial prematurely.[1,2]

Guidelines

National Lipid Association (NLA) – Familial Hypercholesterolemia (FH)

In 2011, the NLA published guidelines for the screening, diagnosis, and management of pediatric and adult patients with FH.[3] The guidelines were published prior to the availability of Juxtapid. FH encompass a group of genetic defects that cause severe elevations in LDL-C levels, as well as other lipid parameters. FH 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 FH include mutations in LDLR, apolipoprotein B (APOB) or proprotein convertase subtilisin kexin type 9 (PCSK9) genes. Over 1,600 known mutations of the LDLR gene have been documented to cause FH and account for about 85% to 90% of FH cases. Patients with FH may have physical findings such as tendon xanthomas, which may occur at a young age. Individuals with FH 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 FH. 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, 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.

European Atherosclerosis Society – Consensus Panel on FH

In 2014, the European Atherosclerosis Society published recommendations regarding HoFH.[4] 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.[4]

Table 1. Criteria for the diagnosis of HoFH.[4]

- Genetic confirmation of two mutant alleles at the LDLR, APOB, 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; APOB – 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.[4] 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. Regression in cutaneous xanthomas has also been noted. AEs of apheresis include hypotension, abdominal pain, nausea, hypocalcemia, iron-deficiency anemia and allergic reactions. The benefits and AEs of Juxtapid are discussed. It is mentioned that in a trial involving

patients with HoFH, Juxtapid at maximally tolerated doses, in addition to standard of care including LDL apheresis, reduced plasma LDL-C and apolipoprotein B levels by around -50% at Week 26; lipoprotein(a) was reduced by approximately -15% at this timepoint. Frequent AEs include GI symptoms and liver fat accumulation. Elevations in alanine aminotransaminase (ALT) three times the upper limit of normal was noted in approximately one-third of patients. Accumulation of liver fat was also noted. Juxtapid is recommended therapy for HoFH patients following use of the highest tolerated dose of statins, and additional lipid modifying therapies, include LDL apheresis.

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. 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. All approvals are provided for 12 months in duration. The criteria apply to patients initiating therapy and to those currently receiving Juxtapid.

Documentation: None required.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

3. **Homozygous Familial Hypercholesterolemia (HoFH) [Initial and Continuing Therapy].** Approve Juxtapid for 12 months if the patient meets the following criteria (A, B, C, D, and E):
   43. The patient is aged ≥ 18 years; AND
   44. The patient meets one of the following (i, ii, iii or iv):
      i. The patient has had 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. The patient has an untreated low-density lipoprotein cholesterol (LDL-C) level > 500 mg/dL (prior to treatment with antihyperlipidemic agents); OR
      iii. The 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. The patient has clinical manifestations of HoFH (e.g., cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma); AND
   45. The patient meets one of the following (i and ii):
      i. The patient has tried Repatha (evolocumab injection for SC use) and has had an inadequate response according to the prescribing physician; OR
      ii. The patient is known to have two LDL-receptor negative alleles; AND
   46. The patient meets one of the following criteria (i or ii):
      i. The 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 the LDL-C level 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 [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) 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); AND
   47. Juxtapid 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

Juxtapid 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.)

142. **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 studied concomitantly with Juxtapid therapy.

143. **Use of Juxtapid in Patients with Heterozygous Familial Hypercholesterolemia (HeFH).** The safety and effectiveness of Juxtapid have not been establsished in patients with hypercholesterolemia who do not have HoFH, including those with HeFH.[1]

144. **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]

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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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

79. 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 ≥ 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:

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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PRIOR AUTHORIZATION POLICY

POLICY: Human Immunodeficiency Virus – Trogarzo™ (ibalizumab-uiyk injection for intravenous use – Theratechnologies)

REVIEW 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.)

81. 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]

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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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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PRIOR AUTHORIZATION POLICY

POLICY: Hyperlipidemia – 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

80. 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).

4. Heterozygous Familial Hypercholesterolemia (HeFH). Approve for 1 year if the patient meets the following criteria (A, B, and C):

48. The patient is ≥ 18 years of age; AND

49. 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

50. 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

Nexletol 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.)

83. 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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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™ (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 $\geq$ 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 Indications

81. 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).

5. Heterozygous Familial Hypercholesterolemia (HeFH). Approve for 1 year if the patient meets the following criteria (A, B, and C):

51. The patient is ≥ 18 years of age; AND

52. 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

53. 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

Nexlizet 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. 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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313. 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.

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)

REVIEW DATE: 01/15/2020

OVERVIEW

Lovaza and Vascepa are indicated as an adjunct to diet to reduce triglyceride (TG) levels in adults with severe (≥ 500 mg/dL) hypertriglyceridemia.[1,2] Vascepa is also indicated as an adjunct to maximally tolerated statin therapy to 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. Lovaza is a combination of ethyl esters of omega-3 fatty acids, principally eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).[1] Vascepa is an ethyl ester of the omega-3 fatty acid EPA.[2]

Clinical Efficacy

Vascepa has data regarding CV outcomes.[2,3] REDUCE-IT was a multicenter, randomized, double-blind, randomized, placebo-controlled, event-driven trial that investigated the effects of Vascepa plus statin therapy vs. placebo plus statin therapy on CV outcomes in a group of patients with established CV disease (70%) or with diabetes and other risk factors (30%), among patients with elevated TG levels (median, 215 mg/dL) and relatively well-controlled LDL-C levels (median, 75 mg/dL) [n = 8,179]. The median duration of follow-up was 4.9 years. At baseline, 93% of patients were receiving moderate- to high-intensity statin therapy. Patients continued to receive statin therapy during the trial. From baseline to Year 1, the median change in TG levels was a decrease of -18.3% among patients in the Vascepa group vs. a 2.2% increase for those given placebo. The median change in LDL-C levels from baseline was an increase of 3.1% in the Vascepa group vs. a 10.2% increase among patients randomized to receive placebo. A primary endpoint event (a composite of CV death, nonfatal myocardial infarction [MI], nonfatal stroke, coronary revascularization or unstable angina) occurred in 17.2% of patients given Vascepa compared with 22.0% of patients given placebo.

Guidelines/Scientific Statements

Several guidelines are available that discuss the management of elevated TG values.[4-7] Therapeutic lifestyle changes (e.g., proper nutrition, weight loss, exercise) can have a great impact on reducing TG levels. The guidelines emphasize that many agents are available to reduce TG levels, including fibrates, niacin products, and statins. Agents with a complementary mechanism of action can also be considered in some circumstances.

The American Diabetes Association (ADA) Standards of Care regarding CV disease and risk management were updated in January 2020 to include a recommendation that Vascepa be considered for patients with diabetes and atherosclerotic cardiovascular disease (ASCVD) or other cardiac risk factors on a statin with controlled LDL-C levels, but with elevated TG levels (135 to 499 mg/dL) to reduce CV risk.[8]

In 2019, the National Lipid Association (NLA) published a scientific statement regarding Vascepa.[9] 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).

Other Uses with Supportive Evidence

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.[8-9] 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.[10,11]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of omega-3 fatty acid products (Lovaza and Vascepa). All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of **Vascepa** is recommended in those who meet the following criteria:

FDA-Approved Indication

28. Cardiovascular Risk Reduction in Patients with Elevated Triglycerides. Approve Vascepa for 3 years if the patient meets all of the following criteria (A, B and C):

A) The patient meets one of the following (i or ii):

i. The patient has established cardiovascular disease.
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. The patient has diabetes and, 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 Vascepa, the patient has a fasting baseline triglyceride level ≥ 150 mg/dL; AND

C) The patient meets one of the following criteria (i or ii):

i. The patient is receiving statin therapy; OR

ii. According to the prescriber the patient cannot tolerate statin therapy.

Coverage of **Lovaza** and **Vascepa** is recommended in those who meet the following criteria:

FDA-Approved Indication

29. Hypertriglyceridemia with Triglyceride (TG) Levels ≥ 500 mg/dL. Approve Lovaza or Vascepa for 3 years if the patient meets the following criteria (A and B):

A) Prior to initiation of Lovaza or Vascepa, the patient has a fasting baseline triglyceride (TG) level ≥ 500 mg/dL; AND

B) The patient has tried, or is currently receiving, one of the following products: niacin (immediate-release or extended-release), a fibrate (e.g., gemfibrozil, fenofibrate, fenofibric acid), or a statin (e.g., atorvastatin, simvastatin).
Note: 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

30. Hypertriglyceridemia with Triglyceride (TG) Levels of 150 mg/dL to < 500 mg/dL. Approve Lovaza or Vascepa for 3 years if the patient meets the following criteria (A and B):

A) Prior to initiation of Lovaza or Vascepa, the patient has a fasting baseline triglyceride (TG) level of 150 mg/dL to < 500 mg/dL; AND

B) The patient has tried, or is currently receiving, one of the following products: niacin (immediate-release or extended-release), a fibrate (e.g., gemfibrozil, fenofibrate, fenofibric acid), or a statin (e.g., atorvastatin, simvastatin).
Note: 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

Omega-3 fatty acid products (Lovaza and Vascepa) 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. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

146. 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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PRIOR AUTHORIZATION POLICY

POLICY: Hypoactive Sexual Desire Disorder – Addyi™ (flibanserin tablets – Sprout Pharmaceuticals)

REVIEW DATE: 12/11/2019

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] The recommended dose of Addyi is 100 mg by mouth daily at bedtime (QHS). It is dosed at bedtime because administration during the day increases the risk of hypotension, syncope, accidental injury, and central nervous system (CNS) depression (such as somnolence and sedation). 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.

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 approval are provided for the duration noted below.

Automation: None

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

6. Hypoactive Sexual Desire Disorder (HSDD)/Female Sexual Interest/Arousal Disorder (FSIAD).

54. Approve 8 weeks of initial therapy if the patient meets the following criteria (i, ii, iii, iv, v, and vi):

- **i.** The patient is premenopausal; AND
- **ii.** The patient's symptoms of HSDD/FSIAD have persisted for a minimum of 6 months; AND

iii. The patient has had normal sexual desire in the past, prior to the diagnosis of HSDD/FSIAD; AND
iv. The 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.

55. Approve for 6 months of continuation therapy if the patient meets the following criteria (i, ii, and iii):
i. The 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. The patient has not reported any serious or concerning adverse events (e.g., hypotension, syncope, dizziness) while taking Addyi.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Addyi 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.)

147. 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.

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

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PRIOR AUTHORIZATION POLICY

POLICY: Hypoactive Sexual Desire Disorder – Vyleesi™ (bremelanotide subcutaneous injection – AMAG Pharmaceuticals, Inc.)

DATE REVIEWED: 12/11/2019

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.

Vyleesi is a melanocortin receptor agonist.[1] The mechanism by which Vyleesi improves HSDD in women is not known. Melanocortinergic neurons may stimulate dopamine release in the medial preoptic area, an area implicated in the sexual behavior of both sexes.[2] Sexual desire is believed to be regulated by neuromodulators of excitatory pathways (e.g., dopamine, norepinephrine, melanocortins, and oxytocin).

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 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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

82. Hypoactive Sexual Desire Disorder (HSDD)/Female Sexual Interest/Arousal Disorder (FSIAD).

A) Approve 8 weeks of initial therapy if the patient meets the following criteria (i, ii, iii, iv, and v):

- **i.** The patient is premenopausal; AND
- **ii.** The patient's symptoms of HSDD/FSIAD have persisted for a minimum of 6 months; AND
- **iii.** The patient has had normal sexual desire in the past, prior to the diagnosis of HSDD/FSIAD; AND
- **iv.** The 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) Approve for 6 months of continuation therapy if patient meets the following criteria (i and ii):

- **i.** The 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

Vyleesi 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. Postmenopausal Patients. Pivotal trials for Vyleesi included only premenopausal women with acquired, generalized hypoactive sexual desire disorder.[1]

86. 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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PRIOR AUTHORIZATION POLICY

POLICY: Idiopathic Pulmonary Fibrosis and Related Lung Disease – Esbriet® (pirfenidone capsules – Genentech)

REVIEW DATE: 10/02/2019

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 and Esbriet® (pirfenidone capsules and film-coated tablets). 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 = 1247).[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.[10-12]

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] The 2011 ATS/ERS/JRS/ALAT guideline for the diagnosis and management of IPF notes that the accuracy of the diagnosis of IPF increases with multidisciplinary interactions between pulmonologists, radiologists, and pathologists experienced in the diagnosis of interstitial lung disease (ILD).[5] The guidelines also state that the diagnosis of IPF requires exclusion of other known causes of ILD; the presence of a usual interstitial pneumonia pattern on HRCT in patients not subjected to surgical lung biopsy; and specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Esbriet. 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. All approvals are provided for 3 years in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

7. Idiopathic Pulmonary Fibrosis (IPF). Approve if the patient meets the following criteria (A, B, C, and D).
- **56.** The patient is ≥ 40 years of age; AND
- **57.** The agent is prescribed by, or in consultation with, a pulmonologist; AND
- **58.** The forced vital capacity (FVC) is ≥ 40% of the predicted value; AND
- **59.** The 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).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Esbriet 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.)

149. 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.

150. 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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PRIOR AUTHORIZATION POLICY

POLICY: Idiopathic Pulmonary Fibrosis and Related Lung Disease – Ofev® (nintedanib capsules – Boehringer Ingelheim)

DATE REVIEWED: 10/02/2019; selected revision 03/25/2020

OVERVIEW

Ofev, a kinase inhibitor, is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).[1] Also, Ofev is indicated to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease. Ofev is additionally indicated for the treatment of chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype.

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.[11,12] 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 high-resolution computed tomography (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 forced vital capacity (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 ILD (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 high resolution computed tomography (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 forced vital capacity (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] The 2011 guideline for the diagnosis and management of IPF from ATS/ERS/JRS/ALAT notes that the accuracy of the diagnosis of IPF increases with multidisciplinary interactions between pulmonologists, radiologists, and pathologists experienced in the diagnosis of interstitial lung disease (ILD).[5] The guidelines also state that the diagnosis of IPF requires exclusion of other known causes of ILD; the presence of a usual interstitial pneumonia pattern on HRCT in patients not subjected to surgical lung biopsy; and specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy.[5]

In 2017, The European League Against Rheumatism updated the recommendations for the treatment of systemic sclerosis.[13] Ofev is not addressed. Regarding patients with lung involvement, cyclophosphamide

should be considered for the treatment for interstitial lung disease due to systemic sclerosis, especially for patients with progressive interstitial lung disease.

POLICY STATEMENT
Prior authorization is recommended for prescription benefit coverage of Ofev. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ofev, approval requires Ofev to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 3 years in duration unless otherwise noted below.

Automation: None.

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

FDA-Approved Indications

8. **Idiopathic Pulmonary Fibrosis**. Approve for 3 years if the patient meets the following criteria (A, B, C, and D).
   - **60.** The patient is ≥ 40 years of age; AND
   - **61.** The agent is prescribed by or in consultation with a pulmonologist; AND
   - **62.** The forced vital capacity (FVC) is ≥ 40% of the predicted value; AND
   - **63.** 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.

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)** The patient is ≥ 18 years of age; AND
   - **B)** The agent is prescribed by or in consultation with a pulmonologist or a rheumatologist; AND
   - **C)** The forced vital capacity (FVC) is ≥ 40% of the predicted value; AND
   - **D)** The diagnosis is confirmed by high-resolution computed tomography.

10. **Chronic Fibrosing Interstitial Lung Disease.** Approve for 3 years if the patient meets the following criteria (A, B, C and D):
    - **A)** The patient is ≥ 18 years of age; AND
    - **B)** The 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 (ILD) [e.g., rheumatoid arthritis ILD]; exposure-related IDL; and mixed connective tissue disease ILD.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Ofev 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.)

151. 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.

152. 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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PRIOR AUTHORIZATION POLICY

POLICY: Immune Globulin – Atgam® (lymphocyte immune globulin, anti-thymocyte globulin [equine] solution for intravenous use – Pfizer)

DATE REVIEWED: 12/04/2019

OVERVIEW

Atgam is derived from horses immunized with human thymus lymphocytes and is composed of antibodies to a variety of antigens on the surface of lymphocytes.[1] The exact mechanism of action of Atgam has not been determined, but may be due to the depletion of circulating lymphocytes, primarily T-lymphocytes.

Atgam is indicated for the management of allograft rejection in renal transplant patients.[1] When administered with conventional therapy at the time of rejection Atgam increases the frequency of resolution of the acute rejection episode.

Atgam is indicated for the treatment of moderate to severe aplastic anemia in patients unsuitable for bone marrow transplantation.[1] 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.

Guidelines

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.

The British Society of Haematology guidelines for the diagnosis and management of AA recommends immunosuppressive therapy with Atgam (equine ATG) plus cyclosporine for the first-line treatment of non-severe AA patients requiring treatment, severe or very severe AA patients who lack a matched sibling donor, and severe or very severe AA 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 for the Management of Immunotherapy-Related Toxicities (Version 1.2019 – November 14, 2018), recommend Atgam as a treatment option for immunotherapy-related cardiovascular toxicity due to immune checkpoint inhibitor therapy.[6,7]

The NCCN Myelodysplastic Syndromes (MDS) Clinical Practice Guidelines (Version 2.2019 – October 18, 2018) recommend Atgam as a treatment option for the management of lower risk MDS.[7,8] Lower risk is defined as International Prognostic Scoring System (IPSS) category of low or intermediate-1; IPSS-Revised (IPSS-R) category of very low, low, or intermediate; or World Health Organization Prognostic Scoring System (WPSS) category of very low, low, or intermediate. 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.

The NCCN Hematopoietic Cell Transplantation Clinical Practice Guidelines (Version 1.2020 – October 30, 2019) recommend ATG in conjunction with corticosteroids for the management of acute steroid-refractory graft-vs-host disease.[30]

Other Uses With Supportive Evidence

The safety and efficacy of equine ATG for the management of MDS has been assessed in a variety of clinical trials.[9-15] These trials utilized equine ATG from two different manufacturers with different dosing regimens. In each of the trials with Atgam, 40 mg/kg/day for 4 days was used in the management of MDS.[9-11] In a Phase II, open-label trial ATG 40 mg/kg/day for 4 days was administered to 25 adult patients with transfusion-dependent MDS.[9] At a median of 55 days after beginning treatment with ATG, 44% of patients (n = 11/25) became red cell transfusion independent with a median duration of response of 10 months. An open-label study assessed the safety and efficacy of ATG 40 mg/kg/day for 4 days in the treatment of patients (n = 32) with MDS.[10] Patients also received cyclosporine for 6 months and methylprednisolone prior to each dose of ATG. In the 31 evaluable patients, four patients had a complete response and one had a partial response for an overall response rate of 16%. In the subgroup of patients with refractory anemia (RA) or RA with ringed sideroblasts, the overall response rate was 22% (n = 4/18), with three complete and one partial response. In a phase II, open-label study the safety and efficacy of ATG 40 mg/kg/day for 4 days was assessed in 61 MDS patients who were red blood cell transfusion dependent.[11] Within 8 months of treatment with ATG, 34% of the patients (n = 21) became transfusion independent and 80% of these patients (n = 17/21) maintained transfusion independence. In addition, responding patients had significant increases in mean platelet and neutrophil counts compared to non-responders. In the four studies utilizing a formulation of equine ATG not available in the US, the dose administered was 15 mg/kg/day for 5 days.[13-15] In these studies, between 29% and 50% of patients treated with equine ATG had a response to treatment.

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.[16] 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.

The utility of Atgam, as part of a conditioning regimen administered prior to allogeneic hematopoietic stem cell transplant has been assessed in a number of studies.[17-25] In a study including patients with severe aplastic anemia (n = 94), cyclophosphamide and Atgam were administered as the conditioning regimen prior to bone marrow transplant.[17] Atgam 30 mg/kg/day was administered on Days 6, 5, and 4 prior to transplant. The incidence of acute and chronic GVHD was 29% and 32%, respectively and overall survival was 88% after a median of 6 years of follow-up. In a retrospective comparison, the efficacy of a reduced intensity conditioning (RIC) regimen with (n = 34) and without Atgam (n = 110) was assessed in patient undergoing umbilical cord blood or peripheral blood stem cell transplant for acute myeloid leukemia.[18] The RIC included fludarabine and cyclophosphamide. Atgam 15 mg/kg every 12 hours was administered on Days 6, 5, and 4 prior to transplant. No significant difference were found between the two RIC regimens for treatment-related mortality, acute or chronic GVHD. The group treated with Atgam did have a lower risk of relapse. In a retrospective analysis the efficacy of an RIC including cyclophosphamide, fludarabine and 4 days of Atgam 40 mg/kg/day was assessed in patients (n = 56) with bone marrow failure syndrome undergoing peripheral blood hematopoietic cell transplant.[19] Patients in the study had received extensive prior transfusion and had a high prevalence of pretransplant HLA-alloimmunization. During the study, no graft failures occurred, overall survival was 87% after 4.5 years of follow-up, and grade II-IV acute GVHD and chronic GVHD occurred in 52% and 72% of patients, respectively. In a retrospective comparison, the efficacy of equine ATG (n = 20) was compared to rabbit ATG (n = 20) in consecutive patients undergoing bone marrow transplantation for severe aplastic anemia.[20] ATG was used as part of a conditioning regimen with cyclophosphamide. The incidence of acute grade II-IV GVHD (0% vs. 35.2%; p = 0.009) and moderate to severe chronic GVHD (0 vs. 34%; p = 0.04) were lower with rabbit ATG vs. equine ATG, respectively. However, lymphocyte counts were higher with equine ATG and overall survival was

similar between groups. A number of smaller retrospective analyses including 4 to 18 patients has found similar results with the addition of Atgam to conditioning regimens administered prior to hematopoietic cell transplantation.[21-25]

The efficacy of Atgam for the treatment of steroid resistant acute GVHD following allogeneic hematopoietic cell transplant was evaluated in four studies[26-29] In a retrospective study, the efficacy of Atgam was assessed in patients (n = 20) with steroid refractory or dependent acute GVHD.[26] Patients who failed to respond or had early relapse after treatment with high-dose prednisolone (> 2 mg/kg) received Atgam 15 mg/kg/day for 5 consecutive days and tacrolimus. Grade III or IV acute GVHD was present in 90% of the patients (n = 18/20). The overall response rate (ORR) was 70% with 40% of patients (n = 8/20) achieving a complete response (CR) and 30% of patients (n = 6/20) achieving a partial response (PR). Median survival post-treatment was 86.5 days (range, 21 to 1081 days) with seven patients alive at the final assessment. In another retrospective study, the efficacy of Atgam was assessed in patients (n = 58) who either progressed after 3 days of methylprednisolone (2 mg/kg/day) or were unchanged after 7 days of methylprednisolone (2 mg/kg/day).[27] Patients received one of the following Atgam regimens: 40 mg/kg/day for 4 days, 15 mg/kg every other day for a total of 6 days, or 10 – 20 mg/kg/day for 5 to 10 days. Nearly all patients (94%, n = 54/58) had grade III or IV acute GVHD. In the 52 evaluable patients, 8% of patients (n = 4/52) had a CR, 23% of patients (n = 12/52) had a PR, mixed results occurred in 42% of patients (n = 22/52), and 27% of patients (n = 14/52) had stable disease or disease progression. Overall survival was poor, with 90% of patients (n = 52/58) dying a median of 40 days (range, 2 to 741 days) after beginning Atgam therapy. A retrospective analysis evaluated the efficacy of Atgam in patients (n = 79) who developed resistant to or progressed after receiving prednisone 60 mg/m^2 daily (or equivalent) for acute GVHD.[28] Patients received Atgam 15 mg/kg twice daily for 5 days. Grade III and IV acute GVHD occurred in 43% of the patients (n = 34/79). A durable CR, defined as a response lasting at least 28 days, was achieved by 20% of patients (n = 16), a durable PR was achieved by 34% of patients (n = 27), and no response occurred in 42% of patients (n = 33). The Kaplan-Meier estimated 1 year survival was 32% (95% confidence interval: 22%, 42%) with 25 patients alive between 1 and 9 years after treatment. A phase 2/3 trial of an investigational product for steroid-resistant acute GVHD included Atgam as the control arm of the study.[29] A total of 47 patients were randomized to the Atgam arm and received 30 mg/kg every other day for a total of 6 doses. The primary endpoint was patient survival at 180 days post randomization. Patients who had received ≥ 3 days of methylprednisolone (≥ 2 mg/kg/day) were included in the trial. Most patients had grade II or III acute GVHD. Survival probability was 47% at Day 180 with Atgam and 57% of patients (n = 27/47) achieved a CR or PR at a median of Day 22.

Atgam has been utilized as a component of induction therapy for heart and lung transplantation.[31-34] 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.[31] At two years after transplantation, more patients treated with Atgam had acute rejection (28% vs. 9%, respectively; P = 0.002) and bronchiolitis obliterans (23% vs. 6.4%; P = 0.002). 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.[32] 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; P = 0.3601). Finally, an article reviewing immunosuppression in lung transplantation states that approximately 20% of the centers that utilize induction therapy use ATG (horse or rabbit).[33] In a clinical trial, patients undergoing heart transplantation were randomized to Atgam (n = 15) or daclizumab (n = 15) as a component of induction therapy.[34] 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.[35] 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, P < 0.05) 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

83. 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.

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84. Aplastic Anemia. Approve for 1 month if the patient meets the following criteria (A, B, and C).
- **A)** The patient has moderate to severe disease; AND
- **B)** The 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

85. Myelodysplastic Syndrome. Approve for 1 month if the patient meets the following criteria (A, B, and C):
- **A)** The patient has lower risk disease
  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; AND
- **B)** The 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.

86. Immune Checkpoint Inhibitor-Related Toxicities. Approve for 1 month if the patient meets the following criteria (A, B, C, and D):
- **A)** The patient has received at least one immune checkpoint inhibitor.
  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); AND

B) The patient has life-threatening myocarditis, pericarditis, arrhythmias, or impaired ventricular function according to the prescriber; AND

C) The 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.

87. 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.

88. Graft-vs.-Host Disease. Approve for 1 month if the patient meets the following criteria (A, B, and C):

A) The patient has acute disease; AND

B) The 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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Atgam 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.

87. 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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PRIOR AUTHORIZATION POLICY

POLICY: Immune Globulin – Cytogam® (human cytomegalovirus immune globulin liquid – CSL Behring)

DATE REVIEWED: 12/04/2019

OVERVIEW

Cytogam® is an intravenous (IV) formulation consisting of human cytomegalovirus immune globulin.[1] It is an immunoglobulin (IG) G containing a standardized amount of antibody to cytomegalovirus (CMV) indicated for the prophylaxis of cytomegalovirus disease associated with transplantation of kidney, lung, liver, pancreas and heart. In transplants of these organs other than kidney from CMV seropositive donors into seronegative recipients, prophylactic Cytogam should be considered in combination with ganciclovir. The maximum recommended dosage is 150 mg Ig/kg per infusion with a total of 7 infusions. The first infusion should be within 72 hours of transplant followed by infusions done at Week 2, 4, 6, 8, 12, and 16 post-transplant.

Disease Overview

CMV is a herpesvirus, which is spread by direct contact with infectious body fluids, including saliva, tears, and urine.[2] It is a common infection in the US, with approximately 50% of the population seropositive for CMV. The initial infection may be asymptomatic or follow a self-limiting course; this is followed by life-long latency where the virus resides in cells without causing damage or clinical illness. Intermittent shedding of virus may occur without any signs or symptoms. In patients who are immunocompromised, viral reactivation may lead to symptomatic disease that may cause significant morbidity and mortality. In the case of persons who may be exposed to CMV, Cytogam can raise the relevant antibodies to levels sufficient to attenuate or reduce the incidence of serious CMV disease.[1]

Clinical Efficacy

Clinical studies with Cytogam have shown a 50% reduction in primary CMV disease in renal transplant patients and a 56% reduction in serious CMV disease in liver transplant patients.[1] Cytogam prophylaxis was associated with increased survival in liver transplant recipients. Other studies of combined prophylaxis with Cytogam and ganciclovir have shown reductions in the incidence of serious CMV-associated disease in CMV-seronegative recipients of CMV seropositive organs below that expected from one drug alone.

Guidelines

International consensus guidelines (2018) are published recommendations for the management of CMV in solid organ transplantation.[3] The multidisciplinary of experts identify CMV management for prevention, treatment, diagnostics, immunology, drug resistance, and pediatric use. A considerable amount of post-transplant patients develop hypogammaglobulinemia with severe cases showing a significant increased risk of CMV disease. Replacement with Cytogam may prevent CMV disease. The guidelines state Cytogam is recommended for use in specific circumstances, especially in thoracic organs, when used in combination with antivirals. Ganciclovir and valganciclovir are antivirals mentioned for use in universal prophylaxis or preemptive therapies for CMV prevention in solid organ transplant patients. Drug-resistant CMV should be considered when there is persistent or recurrent CMV present during prolonged antiviral therapy. Cytogam is considered an alternative therapy to drug-resistant CMV that may improve antiviral host defenses. The guidelines did note, given the lack of controlled trial data there is not a defined best practice for alternative therapy with drug-resistant CMV. Management strategies in pediatric solid organ transplant patients are similar to the adult recommendations. Cytogam is sometimes used in combination with antiviral prophylactic or preemptive therapy to prevent CMV.

Other Uses with Supportive Evidence

Maternal transmission of CMV to the fetus may occur at any gestation, leading to congenital CMV.[4] A study of 304 pregnant women with a primary CMV infection were offered CMV IG. In the therapy group, 157 women were treated with an average of 2 doses (range 1 to 6) of CMV IG 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 a 1.8 fold (30% vs. 56%) increase in the rate of congenital infection in patients without CMV IG ($P < 0.0001$), along with long-term sequelae ($P < 0.001$).

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

89. 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

90. 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

Cytogam 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.)

88. 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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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

91. 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.

92. 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.

93. 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.

94. 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.

95. Kawasaki Disease. Approve for 3 months if prescribed by or in consultation with a pediatric cardiologist or a pediatric infectious diseases physician.

96. 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

97. Antibody-Mediated Rejection (AMBR) in Transplantation. Approve for 1 year if prescribed by or in consultation with a physician affiliated with a transplant center.

98. 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.

99. 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.

100. 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.

101. 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.

102. 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.

103. 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.

104. 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.

105. 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.

106. 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.

107. 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.

108. 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.

109. 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.

110. 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.

111. 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).

112. 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.

113. 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.

114. 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.

115. 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.

116. 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.

117. 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.

118. 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:

89. Adrenoleukodystrophy. Evidence does not support IVIG use.[18]

90. 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]

91. Amyotrophic Lateral Sclerosis. There is insufficient evidence to recommend IVIG.[18]

92. Anemia, Aplastic. Evidence does not support IVIG use.[22]

93. Asthma. Global Initiative for Asthma (GINA) guidelines for asthma management and prevention do not include recommendations for use of IVIG.[54]

94. 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]

95. Autism. Evidence does not support IVIG use.[18] Well-controlled, double-blind trials are needed.

96. 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.

97. 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.

98. 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.

99. 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]

100. 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.

101. 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.

102. 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.

103. 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]

104. In Vitro Fertilization (IVF). There is insufficient evidence to recommend IVIG administration as part of IVF outcomes.[68]

105. Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes (POEMS) Syndrome. Evidence does not support IVIG use.[18]

106. 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.

107. 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]

108. 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.

109. 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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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

119. 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.

120. 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:

110. 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.

111. 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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PRIOR AUTHORIZATION POLICY

POLICY: Immunologicals – Cinqair® (reslizumab injection for intravenous use – Teva Respiratory)

DATE REVIEWED: 02/12/2020

OVERVIEW

Cinqair is indicated for add-on maintenance treatment of patients with severe asthma ≥ 18 years of age who have an eosinophilic phenotype.[1] Cinqair is not indicated for the treatment of other eosinophilic conditions or for the relief of acute bronchospasm/status asthmaticus. Cinqair should be administered as a 3 mg/kg intravenous (IV) infusion once every 4 weeks by a healthcare professional. Cinqair is a human interleukin (IL)-5 antagonist monoclonal antibody. IL-5 is the main cytokine involved in the growth, differentiation, recruitment, activation, and survival of eosinophils, a type of cell involved in asthmatic inflammation.

Clinical Efficacy

The efficacy of Cinqair was established in four randomized, double-blind, placebo-controlled, multicenter pivotal studies in patients with moderate to severe asthma.[2-4] In three of the studies, patients were required to have baseline blood eosinophil levels ≥ 400 cells/microliter despite therapy with a medium to high dose inhaled corticosteroid (ICS). Cinqair (at the FDA-approved dose) was found to reduce the rate of clinical asthma exacerbations per patient per year compared with placebo. Cinqair also significantly increased forced expiratory volume in 1 second (FEV_1) compared with placebo. In the fourth study that did not require patients to have elevated eosinophils at baseline, FEV_1 increased with Cinqair vs. placebo, but this improvement was not statistically significant. However, a significant improvement in this endpoint was observed in a subgroup of patients with baseline eosinophil levels ≥ 400 cells/microliter. A post-hoc analysis of two pivotal studies evaluated oral corticosteroid use.[13] Therapy with Cinqair resulted in significantly fewer new systemic corticosteroid prescriptions per patient compared with placebo. Total and per-patient systemic corticosteroid burdens were lower in patients receiving Cinqair vs. placebo as well.

Guidelines

The 2019 Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention proposes a step-wise approach to asthma treatment.[5] Patients with persistent symptoms or exacerbations despite a medium-dose ICS/long-acting $beta_2$-agonist (LABA) combination with or without an additional controller, GINA recommends referral of the patient to a specialist with expertise in the management of severe asthma for phenotypic assessment and add-on treatment. Cinqair is listed as an option for add-on therapy in patients ≥ 18 years of age with difficult-to-treat, severe eosinophilic asthma. Higher blood eosinophil levels, more exacerbations in the previous year, adult-onset asthma, and nasal polyposis may predict a good asthma response to Cinqair.

According to the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (2014), 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] Uncontrolled asthma is defined as asthma that

meets one of the following four criteria: poor symptom control, frequent severe exacerbations, serious exacerbations, or airflow limitation. Additionally, patients may also have severe asthma if their asthma worsens upon tapering of corticosteroids.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Cinqair. 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, approval requires Cinqair to be prescribed by or in consultation with a physician who specializes in the condition being treated. Refer to criteria below for approval durations.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

11. Asthma. Approve Cinqair for the duration noted if the patient meets one of the following conditions (A or B):

64. Initial Therapy. Approve Cinqair 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. Cinqair is prescribed by or in consultation with an allergist, immunologist, or pulmonologist; AND

iii. Patient has a blood eosinophil count of ≥ 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, and Nucala.

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/maintenance medication; AND

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-interleukin-5 therapy (e.g., Cinqair, Fasenra, Nucala) used concomitantly with an inhaled corticosteroid for at least 3 consecutive months. Examples of additional asthma controller/maintenance medications are inhaled long-acting $beta_2$-agonists, inhaled long-acting muscarinic antagonists, leukotriene receptor antagonists, 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.

v. Patient's asthma is uncontrolled or was uncontrolled prior to starting any anti-interleukin therapy as defined by ONE of the following (a, b, c, d or e):

a) The patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR

b) The patient experienced one or more asthma exacerbation requiring hospitalization or an Emergency Department (ED) 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's asthma worsens upon tapering of oral corticosteroid therapy.
Note: Examples of anti-interleukin therapies include Cinqair, Fasenra, and Nucala.

65. Patients Continuing Cinqair Therapy. Approve Cinqair for 1 year if the patient meets the following criteria (i, ii, and iii):

i. The patient has already received at least 6 months of therapy with Cinqair; AND
Note: Patients who have received < 6 months of therapy or those who are 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. The patient has responded to Cinqair 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 (ED)/urgent care, or medical clinic visits due to asthma; and decreased requirement for oral corticosteroid therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Cinqair 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.)

153. Concurrent use of Cinqair with Another Anti-Interleukin (IL) Monoclonal Antibody. The efficacy and safety of Cinqair used in combination other anti-IL monoclonal antibodies (e.g., Nucala, Fasenra™ [benralizumab subcutaneous injection], Dupixent® [dupilumab subcutaneous injection]) have not been established.

154. Concurrent use of Cinqair with Xolair® (omalizumab injection for subcutaneous use). Xolair is a recombinant humanized IgG1κ 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.[7] The efficacy and safety of Cinqair in combination with Xolair have not been established.

155. Eosinophilic Esophagitis (EoE) or Eosinophilic Gastroenteritis. In addition to a small pilot study, one randomized, double-blind, placebo controlled study (published) [n =226] evaluated the efficacy of Cinqair in pediatric and adolescent patients with EoE.[8,9] In this study, patients were randomly assigned to receive Cinqair IV infusions of 1 mg/kg, 2 mg/kg, or 3 mg/kg, or placebo at Weeks 0, 4, 8, and 12. At Week 15, peak esophageal eosinophil counts were reduced by a median 24%, 59%, 67%, and 64%, with placebo, Cinqair 1 mg/kg, 2 mg/kg, 3 mg/kg, respectively; 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. Additional, well-controlled trials are needed to determine the role of Cinqair in the treatment of EoE and eosinophilic gastroenteritis.

156. Hypereosinophilic Syndrome (HES). One small pilot study (published) [n = 4] evaluated the safety and efficacy of Cinqair in patients with HES who were refractory to or intolerant of treatment with conventional therapy.[10] A single 1 mg/kg 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. Additional, well-controlled trials are needed to determine the role of Cinqair in the treatment of HES. 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 HES; use of anti-IL-5 approaches for the treatment of HES remains investigational.[13] Corticosteroids are the cornerstone of therapy for several forms of HES. In patients who have idiopathic HES 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 HES, enrollment into an anti-IL-5/anti-IL-5 receptor antibody clinical trial is also recommended as second-line therapy.

157. Nasal Polyps. Cinqair was studied in one double-blind, placebo-controlled, randomized safety and pharmacokinetic study (published) [n = 24] in patients with nasal polyps.[11] 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.[12] The magnitude of this reduction was greater than that observed with the overall study population. However, 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.

158. 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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PRIOR AUTHORIZATION POLICY

POLICY: Immunologicals – Dupixent Prior Authorization Policy

- Dupixent® (dupilumab subcutaneous injection – Regeneron/sanofi-aventis)

REVIEW DATE: 02/12/2020; selected revisions 03/25/2020, 06/03/2020, 06/10/2020, and 07/29/2020

OVERVIEW

Dupixent is an interleukin-4 receptor alpha (IL-4Rα) antagonist indicated for the following uses:[1]

- **Asthma,** as an add-on maintenance treatment in patients ≥ 12 years of age with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma. 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

The efficacy of Dupixent for the treatment of asthma was established in three randomized, double-blind, placebo-controlled, multicenter, pivotal studies in patients with persistent asthma.[2-4] Two of these studies included patients ≥ 12 years of age who had moderate to severe asthma that was uncontrolled despite treatment with a medium- to high-dose inhaled corticosteroid (ICS) and up to two additional controller medications.[2,4] In these studies, Dupixent significant reduced the annual exacerbation rate compared with placebo. 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 sever asthma were able to significantly reduce their oral corticosteroid doses and had reduced exacerbations with Dupixent compared with placebo.[3] Dupixent was associated with a greater oral corticosteroid dose reduction regardless of baseline blood eosinoiphil count.

Atopic Dermatitis
The three pivotal Dupixent studies enrolled adult patients with moderate to severe chronic atopic dermatitis.[1,5,6] Patients' atopic dermatitis 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). The primary efficacy endpoint was a score of 0 (clear) or 1 (almost clear) on the Investigator's Global Assessment (IGA) and a reduction of ≥ 2 points from baseline to Week 16. Dupixent was found to be more effective in achieving the primary endpoint at Week 16 compared with placebo. Two additional studies established the efficacy of Dupixent in patients 6 to 17 years of age.[1,7]

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 2019 Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention proposes a step-wise approach to asthma treatment.[11] Patients with persistent symptoms or exacerbations despite a medium-dose ICS/long-acting beta$_2$-agonist (LABA) combination with or without an additional controller, GINA recommends referral of the patient to a specialist with expertise in the management of severe asthma for phenotypic assessment and add-on treatment. Dupixent is listed as an option for add-on therapy in patients ≥ 12 years of age with severe Type 2 asthma or oral corticosteroid-dependent asthma. Evidence of Type 2 inflammation can include elevated sputum or blood eospinophils, elevated fractional concentration of exhaled nitric oxide (FeNO), the need for maintenance oral corticosteroid therapy, or clinically allergen-driven asthma.

According to the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (2014), 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] Uncontrolled asthma is defined as asthma that meets one of the following four criteria: poor symptom control, frequent severe exacerbations, serious exacerbations, or airflow limitation. Additionally, patients may also have severe asthma if their asthma worsens upon tapering of corticosteroids.

Atopic Dermatitis (AD) Guidelines
European consensus guidelines for the treatment of AD (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 AD, 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
Dupixent is not addressed in current guidelines. A 2014 Joint Practice Parameter on the Diagnosis and Management of Rhinosinusitis and a 2008 (evidence update in 2017) Joint Practice Parameter for the Management of Rhinitis recommend nasal corticosteroids be used in patients with CRSwNP.[17-19] Data demonstrate that nasal corticosteroids decrease nasal polyp size and prevent regrowth of nasal polyps following removal. Short courses of oral corticosteroids are also recommended and endoscopic surgical intervention may be considered as an adjunct to medical therapy in patients with CRS that is not responsive or is poorly responsive to medical therapy. 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]

POLICY STATEMENT
Prior authorization is recommended for prescription benefit coverage of Dupixent. 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, approval requires Dupixent to be prescribed by or in consultation with a physician who specializes in the condition being treated. Refer to criteria below for approval durations.

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 of ≥ 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, Cinqair, and Fasenra.
       - **b)** Patient has oral (systemic) corticosteroid-dependent asthma per 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/maintenance medication; AND

       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-interleukin-5 therapy (e.g., Cinqair, Fasenra, Nucala) or Xolair used concomitantly with an inhaled corticosteroid for at least 3 consecutive months. Examples of additional asthma

controller/maintenance medications are inhaled long-acting beta$_2$-agonists, inhaled long-acting muscarinic antagonists, leukotriene receptor antagonists, 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's asthma is uncontrolled or was uncontrolled prior to starting any anti-interleukin therapy or Xolair as defined by ONE of the following (a, b, c, d or e):
- **a)** The patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR
- **b)** The patient experienced one or more asthma exacerbation 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's asthma worsens upon tapering of oral corticosteroid therapy; AND

Note: Examples of anti-interleukin therapies include Dupixent, Nucala, Cinqair, and Fasenra.

v. Dupixent 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: Patients who have received < 6 months of therapy or those who are 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 Dupixent 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):

66. 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. Dupixent is prescribed by or in consultation with an allergist, immunologist, or dermatologist.

67. 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: Patients who have received < 4 months of therapy or those who are restarting therapy with Dupixent should be considered under criterion 2A (Atopic Dermatitis, Initial Therapy).

ii. Patient has responded to Dupixent 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: Patients who have received < 6 months of therapy or those who are 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 Dupixent 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:

159. Concurrent use of Dupixent with another Anti-Interleukin (IL) Monoclonal Antibody. The efficacy and safety of Dupixent in combination with any other anti-IL monoclonal antibody (e.g., Cinqair, Nucala, Fasenra) have not been established.

160. Concurrent use of Dupixent with Xolair® (omalizumab injection for subcutaneous use). Xolair is a recombinant humanized immunoglobulin G1κ 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. The efficacy and safety of Dupixent used in combination with Xolair have not been established.

161. Eosinophilic Esophagitis. A Phase II study has been conducted evaluating Dupixent for the treatment of eosinophilic esophagitis.[22] Results are not yet available. There is an additional Phase III study that is currently underway in patients with eosinoiphilic esophagitis. Results are anticipated in 2022. The efficacy and safety of Dupixent for the treatment of eosinophilic esophagitis have not been established.

162. 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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PRIOR AUTHORIZATION POLICY

POLICY: Immunologicals – Fasenra™ (benralizumab injection for subcutaneous use – AstraZeneca)

DATE REVIEWED: 02/12/2020

OVERVIEW

Fasenra is indicated for add-on maintenance treatment of patients ≥ 12 years of age with severe asthma who have an eosinophilic phenotype.[1] Fasenra is not indicated for the treatment of other eosinophilic conditions or for the relief of acute bronchospasm/status asthmaticus. Fasenra is an interleukin (IL)-5 receptor alpha-directed cytolytic antagonist monoclonal antibody. It binds directly to the IL-5Rα subunit expressed on the surface of eosinophils and basophils, which *in vitro* has been found to facilitate binding to receptors on immune effector cells, such as natural killer (NK) cells. This results in apoptosis of eosinophils and basophils via antibody-dependent cell-mediated cytotoxicity (ADCC).

Clinical Efficacy

The efficacy of Fasenra was established in three randomized, double-blind, placebo-controlled, multicenter pivotal studies.[2-4] Two asthma exacerbation 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. 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). The third pivotal study was an oral corticosteroid (OCS) reduction study involving adults with severe asthma receiving high-dose ICS/LABA and chronic OCS therapy who had a baseline blood eosinophil level ≥ 150 cells/microliter. At Week 28, significantly more patients receiving Fasenra were able to reduce their OCS dose compared with placebo. A 75% reduction from baseline in the median daily OCS dose was observed with Fasenra vs. a 25% reduction with placebo.

Guidelines

The 2019 Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention proposes a step-wise approach to asthma treatment.[5] Patients with persistent symptoms or exacerbations despite a medium-dose ICS/long-acting beta$_2$-agonist (LABA) combination with or without an additional controller, GINA recommends referral of the patient to a specialist with expertise in the management of severe asthma for phenotypic assessment and add-on treatment. Fasenra is listed as an option for add-on therapy in patients ≥ 12 years of age with difficult-to-treat, severe eosinophilic asthma. Higher blood eosinophil levels, more exacerbations in the previous year, adult-onset asthma, and nasal polyposis may predict a good asthma response to Fasenra.

According to the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (2014), 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] Uncontrolled asthma is defined as asthma that meets one of the following four criteria: poor symptom control; frequent severe exacerbations; serious exacerbations; or airflow limitation. Additionally, patients may also have severe asthma if their asthma worsens upon tapering of corticosteroids.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Fasenra. 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, approval requires Fasenra to be prescribed by or in consultation with a physician who specializes in the condition being treated. Refer to criteria below for approval durations.

Automation: None.

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

FDA-Approved Indications

12. Asthma. Approve Fasenra for the duration noted if the patient meets one of the following conditions (A or B):

68. Initial Therapy. Approve Fasenra 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. Fasenra is prescribed by or in consultation with an allergist, immunologist, or pulmonologist; AND

iii. Patient has a blood eosinophil count of ≥ 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, Nucala, Cinqair.

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/maintenance medication; AND
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-interleukin-5 therapy (e.g., Cinqair, Fasenra, Nucala) used concomitantly with an inhaled corticosteroid for at least 3 consecutive months. Examples of additional asthma controller/maintenance medications are inhaled long-acting beta$_2$-agonists, inhaled long-acting muscarinic antagonists, leukotriene receptor antagonists, 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.

v. Patient's asthma is uncontrolled or was uncontrolled prior to starting any anti-interleukin therapy as defined by ONE of the following (a, b, c, d or e):
a) The patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR
b) The patient experienced one or more asthma exacerbation requiring hospitalization or an Emergency Department (ED) 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's asthma worsens upon tapering of oral corticosteroid therapy.
Note: Examples of anti-interleukin therapies include Fasenra, Cinqair and Nucala.

69. Patients Continuing Fasenra Therapy. Approve Fasenra for 1 year if the patient meets the following criteria (i, ii, and iii):

i. The patient has already received at least 6 months of therapy with Fasenra; AND
Note: Patients who have received < 6 months of therapy or those who are 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. The patient has responded to Fasenra 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 (ED)/urgent

care, or medical clinic visits due to asthma; and decreased requirement for oral corticosteroid therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Fasenra 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.)

163. 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.[7] The annualized rate of acute COPD exacerbations was not reduced with Fasenra compared with placebo (rates of 0.95 and 0.92, respectively). 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) evaluated Fasenra in patients with moderate to very severe COPD (n = 1,120 and n = 1,545 patients with eosinophils ≥ 220 cells/mm^3, respectively).[9] Patients were randomized to receive Fasenra or placebo every 8 weeks (every 4 weeks for the first three doses) for 56 weeks. The annualized COPD exacerbation rates were not statistically significantly reduced with Fasenra vs. placebo in either study. In GALATHEA, the rate ratio as compared with placebo was 0.96 with Fasenra 30 mg and 0.83 with Fasenra 100 mg (P = NS for both comparisons). In TERRANOVA, the rate ratio as compared with placebo was 0.85 with Fasenra 10 mg, 1.04 with Fasenra 30 mg and 0.93 with Fasenra 100 mg (P = NS for all).

164. Concurrent use of Fasenra with Another Anti-Interleukin (IL) Monoclonal Antibody. The efficacy and safety of Fasenra used in combination with other anti-IL monoclonal antibodies (e.g., Nucala, Cinqair, Dupixent® [dupilumab subcutaneous injection]) have not been established.

165. 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.[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. The efficacy and safety of Fasenra used in combination with Xolair have not been established.

166. Hypereosinophilic Syndrome (HES). 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.[10] Patients were randomized to receive Fasenra 30 mg SC or placebo every 4 weeks. The primary endpoint was a reduction of 50% or more in the absolute eosinophil count. At Week 12, 90% of patients receiving Fasenra (n = 9/10) vs. 30% of patients receiving placebo (n = 3/10) achieved the primary endpoint (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 HES.[11] Use of anti-IL-5 approaches for the treatment of HES remains investigational. In patients who have idiopathic HES 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 HES, enrollment into an anti-IL-5/anti-IL-5 receptor antibody clinical trial is also recommended as second-line therapy. Further investigation is warranted.

167. 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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PRIOR AUTHORIZATION POLICY

POLICY: Immunologicals – Nucala® (mepolizumab injection for subcutaneous use – GlaxoSmithKline)

DATE REVIEWED: 02/12/2020

OVERVIEW
Nucala is indicated for add-on maintenance treatment of patients ≥ 6 years of age with severe asthma who have an eosinophilic phenotype.[1] Nucala is also indicated for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA) [formerly known as Churg-Strauss Syndrome]. Nucala is not indicated for the treatment of other eosinophilic conditions or for the relief of acute bronchospasm/status asthmaticus. Nucala is a human interleukin (IL)-5 antagonist monoclonal antibody. IL-5 is the main cytokine involved in the growth, differentiation, recruitment, activation, and survival of eosinophils, a type of cell involved in the inflammation present in patients with asthma and EGPA.

Clinical Efficacy

Asthma
The efficacy of Nucala was established in three randomized, double-blind, placebo-controlled, multicenter pivotal studies in patients ≥ 12 years of age with severe asthma and eosinophilic inflammation despite therapy with an inhaled corticosteroid (ICS) and another maintenance medication.[2-4] In patients with a history of frequent exacerbations, Nucala significantly reduced the rate of clinically significant asthma exacerbations per patient per year compared with placebo. Exploratory subgroup analyses indicated that the efficacy of Nucala improved with larger elevations in blood eosinophil counts. In the oral corticosteroid (OCS) reduction study, eligible patients also required maintenance treatment with OCSs. In this study, significantly more patients receiving SC Nucala were able to reduce their oral glucocorticoid dose compared with placebo at Week 24.

Nucala for use 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.[1] Based on results from a pharmacokinetic/pharmacodynamic trial (n = 36) in the pediatric patient population, a dose of Nucala 40 mg SC every 4 weeks was found to result in a similar exposure as 100 mg SC administered to adults and adolescents.[1,29,31] Additionally, the safety profile of Nucala observed with pediatric patients in this trial was found to be similar to that observed in studies of adults and adolescents.[1,30]

EGPA
The efficacy of Nucala was evaluated in one randomized, placebo-controlled, double-blind, Phase III study which involved patients ≥ 18 years of age with relapsing or refractory EGPA who had received ≥ 4 weeks of a stable corticosteroid dose.[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. All patients had a diagnosis of asthma with eosinophilia. In this patient population, Nucala therapy resulted in significantly more accrued weeks of remission than placebo. Additionally, a higher percentage of patients receiving Nucala were in remission at both Week 36 and Week 48 compared with placebo. The magnitude of improvements observed were larger in patients with baseline eosinophil levels ≥ 150 cells per microliter than in patients with lower baseline levels.

Guidelines

Asthma Guidelines
The 2019 Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention proposes a step-wise approach to asthma treatment.[6] Patients with persistent symptoms or exacerbations despite a medium-dose ICS/long-acting beta$_2$-agonist (LABA) combination with or without an additional controller, GINA recommends referral of the patient to a specialist with expertise in the management of severe asthma for phenotypic assessment and add-on treatment. Nucala is listed as an option for add-on therapy in patients ≥ 12 years of age with difficult-to-treat, severe eosinophilic asthma. Higher blood

eosinophil levels, more exacerbations in the previous year, adult-onset asthma, and nasal polyposis may predict a good asthma response to Nucala.

According to the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (2014), 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.[7] Uncontrolled asthma is defined as asthma that meets one of the following four criteria: poor symptom control, frequent severe exacerbations, serious exacerbations, or airflow limitation. Additionally, patients may also have severe asthma if their asthma worsens upon tapering of corticosteroids.

EGPA Guidelines

Current EGPA guidelines do not address Nucala or the other anti-IL-5 therapies. The 2016 European League Against Rheumatism (EULAR) recommendations for the management of ANCA-associated vasculitis address EGPA.[8] 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.[9] 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.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Nucala. 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, approval requires Nucala to be prescribed by or in consultation with a physician who specializes in the condition being treated. Refer to criteria below for approval durations. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

13. Asthma. Approve Nucala for the duration noted if the patient meets one of the following conditions (A or B):

70. Initial Therapy. Approve Nucala 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. Nucala is prescribed by or in consultation with an allergist, immunologist, or pulmonologist; AND

iii. Patient has a blood eosinophil level of ≥ 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.

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/maintenance medication; AND
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-interleukin-5 therapy (e.g., Cinqair, Fasenra, Nucala) used concomitantly with an inhaled corticosteroid for at least 3 consecutive months. Examples of additional asthma controller/maintenance medications are inhaled long-acting $beta_2$-agonists, inhaled long-acting muscarinic antagonists, leukotriene receptor antagonists, 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.

v. Patient's asthma is uncontrolled or was uncontrolled prior to starting any anti-interleukin therapy as defined by ONE of the following (a, b, c, d or e):
a) The patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR
b) The patient experienced one or more asthma exacerbation requiring hospitalization or an Emergency Department (ED) 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's asthma worsens upon tapering of oral corticosteroid therapy.
Note: Examples of anti-interleukin therapies include Nucala, Cinqair, and Fasenra.

71. Patients Continuing Nucala Therapy. Approve Nucala for 1 year if the patient meets the following criteria (i, ii, and iii):

i. The patient has already received at least 6 months of therapy with Nucala; AND
Note: Patients who have received < 6 months of therapy or those who are 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. The patient has responded to Nucala 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 (ED)/urgent care, or medical clinic visits due to asthma; and decreased requirement for oral corticosteroid therapy.

14. 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):

15. Initial Therapy. Approve Nucala 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. Nucala is prescribed by or in consultation with an allergist, immunologist, pulmonologist, or rheumatologist; AND

iii. Patient has tried therapy with a corticosteroid (e.g., prednisone) for a minimum of 4 weeks; AND

iv. Patient has/had a blood eosinophil level of ≥ 150 cells per microliter within the previous 6 weeks or within 6 weeks prior to treatment with any anti-interleukin-5 therapy; OR
Note: Examples of anti-interleukin-5 therapies include Nucala, Cinqair, and Fasenra.

16. Patients Continuing Nucala Therapy. Approve Nucala for 1 year if the patient meets the following criteria (i and ii)

i. The patient has already received at least 6 months of therapy with Nucala; AND
Note: Patients who have received < 6 months of therapy or those who are restarting therapy with Nucala should be considered under criterion 2A (Eosinophilic Granulomatosis with Polyangiitis, Initial Therapy).

ii. The patient has responded to Nucala 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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Nucala 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.)

168. Atopic Dermatitis. Nucala is not indicated for the treatment of atopic dermatitis.[1] In one small randomized, placebo-controlled, parallel group study (published) [n = 40], mepolizumab 750 mg IV once weekly for 2 weeks significantly reduced peripheral blood eosinophil counts in patients with moderate to severe atopic dermatitis.[10] However, mepolizumab IV therapy did not result in clinical success as assessed by Physician's Global Assessment of Improvement scores compared with placebo. Clinical outcomes (as measured by Scoring Atopic Dermatitis [SCORAD] index), pruritus scoring, and serum thymus and activation-regulated chemokine (TARC) values were also not significantly improved with mepolizumab IV vs. placebo. In the same patient population, mepolizumab IV also did not significantly reduce the macroscopic outcome of the atopy patch test, an *in vivo* model that is used to study the induction of eczema by inhalant allergens in patients with atopic dermatitis.[11] Another small multicenter, randomized, double-blind, placebo-controlled, Phase II trial (published) [n = 34] evaluated the efficacy of SC mepolizumab in patients with moderate to severe atopic dermatitis.[33] Following 16 weeks of therapy, Nucala SC did not demonstrate efficacy, with 11% (n = 2/11) of patients receiving Nucala SC met the primary endpoint of treatment success. Treatment success was defined as an Investigator's Global Assessment (IGA) score of 0 or 1 and at least a 2 grade improvement from baseline. No patients receiving placebo met the primary endpoint.

169. 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) [both published] evaluated Nucala in patients with COPD who had a history of moderate or severe exacerbations despite treatment with inhaled triple therapy (ICS/LAMA/LABA).[12] 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 in the METREX study with an eosinophilic phenotype, the difference between Nucala and placebo was statistically significant (mean annual exacerbation rate of 1.40 vs. 1.71, respectively; rate ratio: 0.82; P = 0.04). Difference in the time to first exacerbation was also only significant in the eosinophilic phenotype subgroup of the METREX study. No other secondary endpoints were significantly improved with Nucala in either study. 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 chronic obstructive pulmonary disease (COPD).[13] 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.

170. **Concurrent use of Nucala with another Anti-Interleukin (IL) Monoclonal Antibody.** The efficacy and safety of Nucala used in combination with other anti-IL monoclonal antibodies (e.g., Cinqair, Dupixent® [dupilumab subcutaneous injection], Fasenra) have not been established.

171. **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 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.[14] 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. 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.[15,16,32] Further investigation is warranted.

172. **Eosinophilic Esophagitis (EoE), Eosinophilic Gastroenteritis, or Eosinophilic Colitis.** Nucala is not indicated for the treatment of eosinophilic EoE, eosinophilic gastroenteritis or eosinophilic colitis.[1] In an open-label, Phase I/II study of mepolizumab IV in four adult patients with EoE, dysphagia, and esophageal strictures, three IV infusions of mepolizumab were found to decrease peripheral blood eosinophil counts (by 6.4-fold from baseline) and percent of CCR3+ cells (by 7.9-fold).[17] One small (n = 11), Phase II, randomized, double-blind, placebo-controlled study that assessed the efficacy of mepolizumab 750 mg IV (administered once weekly for 2 weeks) compared with placebo in patients with EoE experiencing frequent episodes of dysphagia (≥ one episode per week).[18] At 4 weeks, mepolizumab therapy resulted in a significant reduction in esophageal eosinophilia (54% reduction) compared with placebo (5% reduction). Another study evaluated three infusions of either 0.55 mg/kg, 2.5 mg/kg, or 10 mg/kg mepolizumab IV administered every 4 weeks in pediatric patients with EoE (n = 59).[19] No placebo comparator was used. Peak eosinophil counts were reduced to < 5 cells/hpf in 8.8% of the patients; no differences between the three doses of mepolizumab IV were observed. The American College of Gastroenterology clinical guideline (2013) for the diagnosis and management of esophageal eosinophilia and EoE state that further studies utilizing anti-IL-5 therapies are needed to define their role in EoE.[20] They note two trials of mepolizumab IV, but highlight that while eosinophil counts declined, the majority of patients did not achieve complete histologic resolution and in adults symptoms did not improve. A 2014 updated food allergy practice parameter from the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI); and the Joint Council of Allergy, Asthma and Immunology (JCAAI) Joint Task Force addressed the treatment of EoE, but also noted that biologic therapies, including anti-IL-5 therapy, have had varying success and are not recommended for routine use in

patients with EoE.[21] There are no data to support the use of Nucala in patients with eosinophilic gastroenteritis or eosinophilic colitis. Further research is warranted to determine if Nucala has a place in therapy in the treatment of these conditions.

173. Hypereosinophilic Syndrome (HES). Nucala is not indicated for the treatment of hypereosinophilic syndrome.[1] In addition to one small open-label trial, one randomized, double-blind, placebo-controlled, multicenter, Phase II trial (published) [n = 85] evaluated mepolizumab IV therapy in patients with HES (negative for the FIP1L1-PDGFRA fusion gene).[22,23] Mepolizumab 750 mg IV for 36 months resulted in significantly more patients reducing their prednisone dose ≤ 10 mg per day compared with placebo (84% of patients vs. 43% of patients, P < 0.001). In an open-label extension of this study (mean exposure to mepolizumab of 251 weeks), 62% of patients were prednisone-free without other hypereosinophilic syndrome medications for ≥ 12 weeks.[24] SC Nucala has not been studied in this patient population. IV mepolizumab is available from the manufacturer on a compassionate use basis for patients with life-threatening HES who have failed prior therapies.[25] 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. Use of anti-IL-5 approaches for the treatment of HES remains investigational. In patients who have idiopathic HES 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 HES, enrollment into an anti-IL-5/anti-IL-5 receptor antibody clinical trial is also recommended as second-line therapy.

174. Nasal Polyps. There are limited data regarding the use of Nucala in patients with nasal polyps. One small (n = 30), randomized, double-blind study compared mepolizumab 750 mg IV (every 28 days for two doses) with placebo for the treatment of severe nasal polyposis.[26] At Week 8, mepolizumab IV was found to significantly improve the change in the total polyp score from baseline compared with placebo. Non-significant improvements in patients' loss of smell, postnasal drip, and congestion were observed with mepolizumab IV at Week 8 vs. the placebo group; rhinorrhea remained at the same level regardless of treatment. A second randomized, double-blind, placebo-controlled study (n = 105) involved adult patients with recurrent nasal polyposis who required surgery.[27] Patients received either mepolizumab 750 mg IV or placebo Q4W for 6 doses in addition to topical corticosteroids. At Week 25, significantly more patients who received mepolizumab no longer required surgery compared with placebo (30% vs. 10%, respectively). The nasal polyposis visual analog scale (VAS) score and the endoscopic nasal polyp score were also significantly improved with mepolizumab along with several other secondary endpoints. No studies of SC Nucala have been conducted in this patient population. In June 2017, a Phase III study of Nucala in patients with severe bilateral nasal polyps began; results are not yet available.[28]

175. 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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PRIOR AUTHORIZATION POLICY

POLICY: Immunologicals – Xolair® (omalizumab injection for subcutaneous [SC] use – Genentech/Novartis)

DATE REVIEWED: 02/12/2020; selected revision 03/25/2020

OVERVIEW

Xolair is a recombinant humanized immunoglobulin G (IgG)1κ monoclonal antibody which selectively binds to human immunoglobulin E (IgE), thus inhibiting IgE from binding to the surface of mast cells and basophils (at the high-affinity IgE receptor [FcεRI]), and resulting in a decrease of mediators released in the allergic response.[1] Xolair treatment also reduces the number of FcεRI receptors on basophils in atopic patients. Xolair is 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 (ICSs). Xolair decreases the incidence of asthma exacerbations in these patients. Safety and efficacy of Xolair in pediatric patients with asthma aged < 6 years have not been established. Xolair is also indicated for the treatment of adults and adolescents (aged ≥ 12 years) with chronic idiopathic urticaria who remain symptomatic despite H_1 antihistamine treatment. In chronic idiopathic urticaria, Xolair binds to IgE and lowers free IgE levels; subsequently, FcεRI on cells down-regulate. How these effects of Xolair result in an improvement in chronic idiopathic urticaria is not known. Xolair is not indicated for the treatment of other allergic conditions, other forms of urticaria, for relief of acute bronchospasm, or status asthmaticus.

Guidelines

Asthma Guidelines

Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention proposes a step-wise approach to asthma treatment.[2] Patients with persistent symptoms or exacerbations despite a medium-dose ICS/long-acting beta$_2$-agonist (LABA) combination with or without an additional controller, GINA recommends referral of the patient to a specialist with expertise in the management of severe asthma for phenotypic assessment and add-on treatment. Xolair is listed as an option for add-on therapy in patients ≥ 6 years of age with moderate or severe allergic asthma. Blood eosinophil levels ≥ 260 cells per microliter, fractional exhaled nitric oxide (FeNO) ≥20 ppb, allergen-driven symptoms, and childhood-onset asthma may predict a good asthma response to Xolair.

The European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (2014) for the definition, evaluation, and treatment of severe asthma suggest a trial of Xolair in both adults and children with severe allergic asthma.[3] If a trial of Xolair is considered, patients (adults and children ≥ 6 years of age) should have confirmed IgE-dependent allergic asthma that is uncontrolled despite optimal pharmacological and non-pharmacological management and appropriate allergen avoidance and their total serum IgE level should be ≥ 30 IU/mL and < 700 IU/mL. It is also noted that further administration of Xolair is unlikely to be beneficial if a patient does not respond to therapy within the first 4 months of treatment. The ERS/ATS guidelines also provide a definition of severe asthma. 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. Uncontrolled asthma is defined as asthma that meets one of the following four criteria: poor symptom control; frequent severe exacerbations; serious exacerbations; or airflow limitation. Additionally, patients may also have severe asthma if their asthma worsens upon tapering of corticosteroids.

Urticaria Guidelines

Urticaria guidelines 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] also stress the importance of identification and elimination of underlying causes and trigger avoidance followed by pharmacologic treatment to reduce release of mast cell mediators (e.g. histamine) and/or decrease the effect of these mast cell mediators at target organs.[4] Continuous therapy with antihistamines (second generation H_1-antagonists) is recommended as first-line treatment. If symptoms persist following 2 to 4 weeks of initial therapy, the dose of the second generation H_1-antagonist should be increased to up to 4-fold. If symptoms persist an additional 2 to 4 weeks despite the higher dosing, the addition of Xolair may be considered. Cyclosporine is referenced as an add-on therapy to Xolair if there is inadequate control or symptoms are intolerable within 6 months. Short courses of oral corticosteroids may also be considered if needed to control exacerbations. However, long-term use of systemic corticosteroids is not recommended.

In 2014, 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) published a Joint Task Force Practice Parameter on the diagnosis and management of acute and chronic urticaria.[5] This parameter recommends a four-step approach to treatment of chronic urticaria. Initially, trigger avoidance is indicated along with a second generation antihistamine (Step 1). Step 2 includes increasing the dose of the antihistamine; a 2- to 4-fold increase in the FDA-approved dose of the second-generation antihistamine may be effective to achieve symptom control in some patients. Additionally, adding a second non-sedating antihistamine, an H_2 antagonist, a leukotriene receptor antagonist (LTRA), or a first generation antihistamine to be taken at bedtime may also be beneficial. If the

patient's urticarial remains poorly controlled, hydroxyzine or doxepin may be considered as part of Step 3 therapy. Patients with refractory chronic urticaria (Step 4) may consider other alternative therapies, such as Xolair and cyclosporine.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Xolair. 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, initial and continuing approval requires Xolair 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.

Automation: None.

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

FDA-Approved Indications

31. Asthma. Approve Xolair for the duration noted if the patient meets one of the following conditions (A or B):

A) Initial Therapy. Approve Xolair 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. Xolair is prescribed by or in consultation with an allergist, immunologist, or pulmonologist; AND

iii. Patient has a baseline (prior to treatment with Xolair or anti-interleukin-4/13 therapy [Dupixent]) immunoglobulin E (IgE) level ≥ 30 IU/mL; AND

iv. The patient has a baseline (prior to treatment with Xolair) 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: Examples of perennial aeroallergens are house dust mite, animal dander, cockroach, feathers, and mold spores. Examples of seasonal aeroallergens are grass, pollen, and weeds.

v. 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/maintenance medication; AND

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 inhaled corticosteroid for at least 3 consecutive months. Examples of additional asthma controller/maintenance medications are inhaled long-acting beta$_2$-agonists, inhaled long-acting muscarinic antagonists, leukotriene receptor antagonists, 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.

vi. Patient's asthma is uncontrolled or was uncontrolled prior to receiving any Xolair or anti-IL-4/13 therapy (Dupixent) therapy as defined by ONE of the following (a, b, c, d, or e):

a) The patient experienced two or more asthma exacerbations requiring treatment with systemic corticosteroids in the previous year; OR

b) The patient experienced one or more asthma exacerbation requiring hospitalization or an Emergency Department (ED) 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's asthma worsens upon tapering of oral corticosteroid therapy.

B) Patients Continuing Xolair Therapy. Approve Xolair for 1 year if the patient meets the following criteria (i, ii, and iii):

i. The patient has already received at least 4 months of therapy with Xolair; AND
Note: Patients who have received < 4 months of therapy or those who are 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. The 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 (ED)/urgent care, or medical clinic visits due to asthma; decreased reliever/rescue medication use; and improved lung function parameters.

32. **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 Xolair for 4 months if the patient meets the following criteria (i, ii, and iii):
        - **i.** Patient is ≥ 12 years of age; AND
        - **ii.** Xolair is prescribed by, or in consultation with, an allergist, immunologist, or dermatologist; AND
        - **iii.** 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.
          Note: Examples of non-sedating H_1 antihistamine therapy are cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine.
    - **B)** Patients Continuing Xolair Therapy. Approve Xolair for 1 year if the patient meets the following criteria (i and ii):
        - **i.** The patient has already received at least 4 months of therapy with Xolair; AND
          Note: Patients who have received < 4 months of therapy or those who are restarting therapy with Xolair should be considered under criterion 2A (Chronic Idiopathic Urticaria, Initial Therapy).
        - **ii.** The patient has responded to therapy (e.g., decreased severity of itching, decreased number and/or size of hives) 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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Xolair 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. **Atopic Dermatitis (AD).** There have been several case series/reports and two small randomized, double-blind, placebo-controlled pilot studies evaluating the efficacy and safety of Xolair for the treatment of patients with AD.[6,7] Efficacy data have been mixed. One systematic review and meta-analysis reported that of the studies reviewed (n = 103 patients total), 43% of patients achieved an excellent clinical response with Xolair, while 27.2% of patients had satisfying results and another 30.1% had no clinical change or worsening of their disease. However, these data are difficult to interpret due to the very small sample sizes in each case series/report and the non-controlled, non-randomized design of the majority of the available studies. Additional larger, well-designed clinical trials are needed to determine if Xolair has a role in the treatment of AD. AD guidelines from the American Academy Dermatology (AAD) [2014] note that data are limited to determine if Xolair is efficacious in the treatment of AD.[8] These guidelines do not make a recommendation regarding Xolair use in this patient population. European consensus guidelines for the treatment of AD (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) also note the mixed data and state that they cannot recommend Xolair for the treatment of AD.[9] There is currently one randomized, double-blind, placebo controlled study evaluating Xolair for the treatment of pediatric AD (Atopic Dermatitis Anti-IgE Paediatric Trial [ADAPT]).[10] This trial is ongoing and results are not yet available.

2. **Chronic Rhinosinusitis.** A small study assessed the effects of Xolair in patients (n = 14) with chronic rhinosinusitis.[11] The majority of patients had severe and refractory disease and presented with nasal polyposis; all had undergone endoscopic sinus surgery. After 6 months Xolair-treated patients showed reduced sinus inflammation (as determined by computed tomography [CT] imaging) while placebo-treated patients showed no change in inflammation; however, the net difference between groups was not statistically significant. A small, single arm study (n = 13) also demonstrated efficacy of Xolair in improving symptoms in patients with chronic rhinosinusitis with nasal polyps.[12] Further study is warranted. The 2015 Clinical Practice Guideline: Adult Sinusitis from the American Academy of Otolaryngology (AAO) does not mention Xolair or anti-IgE therapy in its recommendations.[13]

3. **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 very limited case reports describing the combination use of Nucala and Xolair for severe asthma as well as off-label indications.[14-16] Further investigation is warranted.

4. **Eosinophilic Gastroenteritis (EG), Eosinophilic Esophagitis (EE), or Eosinophilic Colitis.** There are limited and conflicting data on the use of Xolair for the treatment of eosinophilic gastrointestinal conditions. In a case series evaluating patients with eosinophil-associated gastrointestinal disorders, Xolair was effective in decreasing absolute eosinophil count, allergen skin test wheal and erythema responses, and symptom scores.[17] Subsequently, a small (n = 15), open-label, single-arm, unblinded study (published) evaluated Xolair for the treatment of patients 12 to 75 years of age with EE.[18] Following 12 weeks of Xolair therapy (dose calculated in mg/kg per IU IgE units/mL), tissue IgE levels were significantly reduced in 13 of the 15 patients, with full remission (defined as histologic and clinical improvement) present in 33% of patients. Conversely, a prospective, randomized, double-blind, placebo-controlled trial (n = 30) also examined the effects of Xolair in patients 12 to 60 years of age with EE who were either refractory to or relapsed after a trial of topical corticosteroids.[18,19] Patients received either Xolair or placebo every 2 to 4 weeks for 16 weeks (dose of Xolair based on weight and serum IgE level). Xolair therapy was not found to improve the symptoms of EE (dysphagia scores) or eosinophil counts in biopsy samples when compared with placebo. An additional case series including two patients with multiple food allergies and EE reported an improvement in patient symptoms with Xolair therapy, but did not find an improvement in esophageal endoscopy and histology in short-term follow-up.[20] The 2013 American College of Gastroenterology guidelines for the diagnosis and management of esophageal eosinophilia and EE do not recommend Xolair therapy for these conditions; the guidelines note that Xolair was ineffective in a case series involving two patients (referenced above). It is recognized that corticosteroids (systemic or topical administered by swallowing a formulation for inhalation) are the standard treatment for management of both EG and EE.[21,22] Adequate controlled clinical studies have not been conducted in patients less than 12 years of age with EG, EE, or eosinophilic colitis. A 2014 updated food allergy practice parameter from the AAAAI,

ACAAI, and JCAAI Joint Task Force also addresses EE and EG, but does not address Xolair as a treatment for these conditions.[23]

5. **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.[24] 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.

6. **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.[25] 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.[26] 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.[27-30] 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.[31,32] Guidelines for the diagnosis and management of food allergy in the US (published in 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.[33] Allergen avoidance and use of antihistamines are recommended for treatment of food-induced allergic reactions. The updated food allergy practice parameter from the AAAAI, ACAAI, and JCAAI Joint Task Force (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.[23] 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.

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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PRIOR AUTHORIZATION POLICY

POLICY: Increlex® (mecasermin [rDNA origin] for subcutaneous injection – Ipsen Biopharmaceuticals/Hospira)

DATE REVIEWED: 10/10/2018

OVERVIEW

Increlex is indicated for the long-term treatment of growth failure in children with severe primary insulin-like growth factor-1 (IGF-1) deficiency (Primary IGFD) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH.[1] Severe Primary IGFD is defined by:

- Height standard deviation score (SDS) ≤ -3.0 and
- basal IGF-1 SDS ≤ -3.0 and
- normal or elevated GH

Increlex is given by subcutaneous (SC) injection twice daily, shortly before or after a meal or snack. It is a limitation of use that Increlex is not a substitute for GH for approved GH indications. Increlex is not indicated in secondary forms of IGF-1 deficiency, such as GH deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids and is not a substitute for GH (somatropin) therapy.[1] Thyroid and nutritional deficiencies should be corrected before initiating Increlex treatment.

Disease Overview

IGF-1 is the principal hormonal mediator of growth hormone action.[3] Under normal circumstances, GH 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, which is homologous to the insulin 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 IGFD is a group of disorders characterized by decreased IGF production with normal or increased GH secretion.[2] Three distinct molecular abnormalities have been identified as causes of primary IGFD: 1) mutations or gene deletions of the GH receptor gene; 2) mutations affecting the post- GH receptor (GHR) 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 GH deficient, and do not respond

adequately to exogenous GH treatment.[1-2] Once a diagnosis of severe primary IGFD 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 IGFD.[1] 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 for change from pre-Tx*		<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 1 year in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

33. Severe Primary Insulin-Like Growth Factor-1 (IGF-1) Deficiency (Primary IGFD) in a Child. Approve for 1 year if the patient meets ONE of the following conditions (A or B):

C) Initial Therapy or Patient has been on Increlex less than 1 Year. Approve for 1 year if the patient meets ALL of the following conditions (i, ii, iii, and iv):

v. Height standard deviation score is ≤ -3.0 at baseline; AND
Note: An online tool to assess height SDS is available at: http://www.increlex.com/hcp-growth-tracking-tool.asp

vi. 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.

vii. Growth hormone concentration is normal or increased at baseline; AND

viii. Increlex is prescribed by or in consultation with a pediatric endocrinologist.

D) Patient has been receiving Increlex for at least 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 (Note: Patients are reviewed annually for growth rate.); AND

ii. The epiphyses are open.

Increlex is indicated for growth failure in children with severe primary IGFD, defined by height standard deviation score ≤ -3.0 and basal IGF-1 standard deviation score ≤ -3.0 and normal or elevated growth hormone.[1] However, the reporting laboratory may not report the SDS for IGF-1; therefore SDS is required to be below the limit of normal but is not required to be ≤ -3 SDS. Studies have evaluated the efficacy of Increlex in patients with severe Primary IGFD.[1] Over the course of 8 years in studies evaluating patients treated with Increlex, mean height velocity (SD) ranged from 8.0 (2.2) cm/year to 4.3 (1.1) cm/year. Treatment should continue until the epiphyses fuse indicating full growth potential has been achieved.[3] In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

34. Growth Hormone (GH) Gene Deletion in a Child who has Developed Neutralizing Antibodies to GH. Approve for 1 year if the patient meets ONE of the following conditions (A or B):

C) Initial Therapy or Patient has been on Increlex less than 1 Year. Approve if Increlex is prescribed by or in consultation with a pediatric endocrinologist.

D) Patient has been receiving Increlex for at least 1 Year. Approve for continuation of therapy if the patient meets BOTH of the following conditions (i and ii):

iii. The patient's height has increased by ≥ 4 cm/year in the most recent year (Note: Patients are reviewed annually for growth rate.); AND

iv. The epiphyses are open.

Over the course of 8 years in studies evaluating patients treated with Increlex, mean height velocity (SD) ranged from 8.0 (2.2) cm/year to 4.3 (1.1) cm/year.[1] In these studies, 11% of the patients (n = 7) had GH gene deletion. Treatment should continue until the epiphyses fuse indicating full growth potential has been achieved.[3] In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Increlex 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.)

3. 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.

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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PRIOR AUTHORIZATION POLICY

POLICY: Infectious Disease – Daraprim® (pyrimethamine tablets – Vyera Pharmaceuticals)

REVIEW DATE: 10/02/2019, effective 01/01/2020

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 virus (HIV) [last reviewed June 26, 2019] recommend pyrimethamine as the drug of choice for treatment of *Toxoplasma gondii* encephalitis. Pyrimethamine is recommended as an option for: primary prophylaxis and chronic maintenance treatment (secondary 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

18. Treatment of Toxoplasmosis. Approve Daraprim for 1 year.

Other Uses with Supportive Evidence

19. **Cystoisoporiasis (formerly known as isosporiasis) – Chronic Maintenance Treatment (Secondary Prophylaxis).** Approve Daraprim for 1 year if the patient has tried one other therapy for this condition or has contraindications to that therapy.

20. **Cystoisoporiasis (formerly known as isosporiasis) – Treatment.** Approve Daraprim for 1 year if the patient has tried one other therapy for this condition or has contraindications to that therapy.

~~21.~~ ***Pneumocystis*** **Pneumonia – Chronic Maintenance Therapy (Secondary Prophylaxis).** Approve Daraprim for 1 year if the patient has tried one other therapy for this condition or has contraindications to that therapy.

~~22.~~ ***Pneumocystis*** **Pneumonia – Primary Prophylaxis.** Approve Daraprim for 1 year if the patient has tried one other therapy for this condition or has contraindications to that therapy.

~~23.~~ ***Toxoplasma gondii*** **Encephalitis – Chronic Maintenance Therapy (Secondary Prophylaxis).** Approve Daraprim for 1 year if the patient has tried one other therapy for this condition or has contraindications to that therapy.

~~24.~~ ***Toxoplasma gondii*** **Encephalitis – Primary Prophylaxis.** Approve Daraprim for 1 year if the patient has tried one other therapy for this condition or has contraindications to that therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Daraprim 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.)

5. **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).

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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PRIOR AUTHORIZATION POLICY

POLICY: Infectious Disease – Pretomanid tablets (Global Alliance for TB Drug Development/Mylan Laboratories)

REVIEW DATE: 10/16/2019

OVERVIEW

Pretomanid 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 it's used with drugs other than Sirturo and linezolid have not been established. The duration of therapy is 26 weeks but it may be extended beyond 26 weeks if necessary (therapy could be extended to 9 months in the clinical trial).

Globally, drug-resistant TB is a public health crisis; 3.5% of new TB cases are multidrug-resistant/rifampicin-resistant TB (MDR/RR-TB) and of these cases, 8.5% are XDR-TB.[2,3] Treatment success has increased slightly but remains low, at 52% for MDR/RR-TB and 34% for XDR-TB.

Guidelines

Pretomanid has not been added to guidelines. The World Health Organization (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.[4] Treatment of MDR/RR-TB should be started with at least four TB agents 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 agents 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. Because of the specialized skills required for evaluation and diagnosis of patients with these conditions, as well as monitoring required for adverse events and efficacy, approval requires Pretomanid to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 9 months in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

35. Tuberculosis, Pulmonary Extensively Drug Resistant or Treatment-Intolerant or Nonresponsive Multidrug-Resistant. Approve Pretomanid for 9 months if the patient meets the following criteria (A, B, and C):
- **C)** The 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)** Pretomanid is prescribed by, or in consultation with. an infectious diseases specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Pretomanid 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. 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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PRIOR AUTHORIZATION POLICY

POLICY: Infectious Disease – Sirturo® (bedaquiline fumarate tablets – Janssen Therapeutics, Division of Janssen Products LP)

REVIEW DATE: 10/16/2019

OVERVIEW

Sirturo is indicated, as part of a combination therapy in the treatment of adult and pediatric patients (12 to < 18 years of age and weighing ≥ 30 kg) with pulmonary multidrug-resistant tuberculosis (MDR-TB). Sirturo should be used when an effective treatment regimen cannot otherwise be provided. Sirturo should not be used for latent infections due to *Mycobacterium tuberculosis*, drug-sensitive tuberculosis, extra-pulmonary tuberculosis, and infections caused by non-tuberculous mycobacteria. The duration of therapy for MDR-TB is 24 weeks. When Sirturo is used in combination with Pretomanid 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 MDR-TB, the duration of therapy is 26 weeks (or extended to 9 months).

Globally, drug-resistant tuberculosis (TB) is a public health crisis; 3.5% of new TB cases are multidrug-resistant/rifampicin-resistant TB (MDR/RR-TB) and of these cases, 8.5% are extensively drug-resistant TB (XDR-TB).[2,3] Treatment success has increased slightly but remains low, at 52% for MDR/RR-TB and 34% for XDR-TB.

Guidelines

The World Health Organization (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.[4] Treatment of MDR/RR-TB should be started with at least four TB agents 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 agents 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. Because of the specialized skills required for evaluation and diagnosis of patients with these conditions, as well as monitoring required for adverse events and efficacy, approval requires Sirturo to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 9 months in duration unless otherwise noted below.

Automation: None.

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

FDA-Approved Indications

36. Tuberculosis, Pulmonary Multidrug-Resistant or Extensively Drug-Resistant. Approve Sirturo for 9 months if the patient meets the following criteria (A, B, and C):
- **F)** The patient is ≥ 12 years of age and weighs ≥ 30 kg; AND
- **G)** Sirturo is prescribed as part of a combination regimen with other anti-tuberculosis agents; AND
- **H)** Sirturo is prescribed by, or in consultation with, an infectious diseases specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Sirturo 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.)

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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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 $\pm$ 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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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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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 – Adalimumab Products

- Humira® (adalimumab for subcutaneous injection – AbbVie)

DATE REVIEWED: 11/06/2019; selected revision 06/10/2020

OVERVIEW

Adalimumab products are tumor necrosis factor inhibitors (TNFis) approved for the following uses:[1]

- **Rheumatoid arthritis** (RA), to reduce the signs and symptoms, induce major clinical response, inhibit the progression of structural damage, and improve physical function in adult patients with moderately to severely active disease. Humira can be used alone or in combination with methotrexate (MTX) or other conventional synthetic disease-modifying antirheumatic drugs (DMARDs); AND
- **Juvenile idiopathic arthritis** (JIA), for reducing signs and symptoms of moderately to severely active polyarticular disease in patients 2 years of age and older. Humira can be used alone or in combination with MTX; AND
- **Psoriatic arthritis** (PsA), for reducing the signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function. Humira can be used alone or in combination with conventional synthetic DMARDs; AND
- **Ankylosing spondylitis** (AS), for reducing signs and symptoms in patients with active disease; AND
- **Plaque psoriasis**, for the treatment of adults with moderate to severe chronic disease who are candidates for systemic therapy or phototherapy and when other systemic therapies are medically less appropriate; AND
- **Crohn's disease**:
  - for reducing signs and symptoms and inducing and maintaining clinical remission in adults with moderately to severely active disease who have had an inadequate response to conventional therapy, including for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to Remicade® (infliximab intravenous [IV] infusion); AND
  - for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine (6-MP), or MTX; AND
- **Ulcerative colitis** (UC), for inducing and sustaining clinical remission of moderately to severely active disease in adults who do not respond to corticosteroids or other immunosuppressive drugs such as azathioprine or 6-mercaptopurine. However, efficacy has not been established in patients with UC who have lost response or were intolerant to another TNF inhibitor (TNFi); AND
- **Hidradenitits suppurativa** (HS), for the treatment of moderate to severe disease in patients ≥ 12 years of age; AND
- **Uveitis**, in patients ≥ 2 years of age with noninfectious intermediate, posterior, and panuveitis.

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 psoriasis, psoriatic arthritis, inflammatory bowel disease, and RA. Increased levels of TNF are found in the synovial fluid of patients with RA, JIA, AS, and PsA; TNF has an important role in both the pathologic inflammation and the joint destruction that are characteristic of this disease. In psoriasis, increased levels of TNF are found in the blood and skin lesions. Adalimumab products binds to TNFα and inhibits binding of TNFα with its receptors.

Guidelines

TNFis feature prominently in guidelines for treatment of inflammatory conditions.

- **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).[2]
- **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).[3] 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.
- **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.
- **Juvenile Idiopathic Arthritis (JIA):** In polyarticular disease, the 2019 ACR recommendations propose initial DMARD treatment with a conventional synthetic DMARD such as MTX in most patients prior to a TNFi.[3] In those who are secondary nonresponders to a TNFi, a second TNFi may be tried; however, a non-TNF biologic is recommended for primary nonresponders. TNFis may also be used as second- or third-line treatment for systemic JIA.[10]
- **Plaque Psoriasis:** Guidelines from the American Academy of Dermatologists (AAD) and National Psoriasis Foundation (NPF) [2019] recommend adalimumab 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 PsA and in those who were previously treated with an oral therapy.[7]
- **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 (budesonide tablets); oral or intravenous systemic corticosteroids, Entyvio (vedolizumab injection), Xeljanz (tofacitinib tablets), or TNFis (adalimumab, Simponi SC, infliximab).[8] 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).[9] Other treatment options include maintenance probiotics, oral or topical budesonide, anti-inflammatory drugs (e.g., mesalamine), or immunosuppressive drugs (e.g., Remicade).
- **Ocular Inflammatory Disorders:** The American Academy of Ophthalmology (AAO) [2014] note that Humira 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).[11] Humira should be considered second-line in vision-threatening JIA-associated uveitis when MTX 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). Humira may also be considered in other patients who have vision-threatening or corticosteroid-dependent disease who have failed first-line therapies. Humira should be considered as a second-line immunomodulatory agent for severe ocular inflammatory conditions including chronic and severe scleritis.

- **Behcet's Disease:** 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.[11]
- **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.[13] Other systemic therapies include cyclosporine, MTX, azathioprine, cyclophosphamide, mycophenolate mofetil, Remicade, Enbrel, and Humira. In case reports, TNFis have been effective.
- **Sarcoidosis:** Recommendations for best practice in the management of pulmonary and systemic sarcoidosis recommend glucocorticoids as first-line therapy.[14] 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., MTX, azathioprine, leflunomide). If these agents fail or cause toxicity, Humira, Remicade, cyclophosphamide, or mycophenolate mofetil are proposed.

Safety

Adalimumab products have 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; periodically during therapy, patients should be assessed for latent TB infection. Patients should also be monitored for signs and symptoms of infection during and after treatment with an adalimumab product, and if a serious infection or sepsis develops, discontinue therapy. Lymphoma and other malignancies have been reported in children and adolescents taking TNFis. There have also been reports of hepatosplenic T-cell lymphoma in adolescent and young adults treated with TNFis such as adalimumab products.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of adalimumab products. Because of the specialized skills required for evaluation and diagnosis of patients treated with adalimumab products as well as the monitoring required for adverse events (AEs) 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 for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of adalimumab products [Humira] is recommended in those who meet one the following 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.** The 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 (e.g., Cimzia [certolizumab pegol SC injection], an etanercept product, an infliximab product, Simponi [golimumab SC injection], Simponi Aria [golimumab IV infusion], Actemra [tocilizumab IV infusion; tocilizumab SC injection], Kevzara [sarilumab SC injection], Kineret [anakinra SC injection], Orencia [abatacept IV infusion; abatacept SC injection], and a rituximab product). These patients who have already tried a biologic for RA 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)** Patients Currently Receiving an Adalimumab Product. 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 an adalimumab product.

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 prescribed by or in consultation with a rheumatologist.
- **B)** Patients Currently Receiving an Adalimumab Product. 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, or improvement in 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 adalimumab product.

E) 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.** The patient is ≥ 6 years of age; AND
  - **ii.** The patient meets ONE of the following conditions (a, b, c, or d):
    1. The patient has tried or is currently taking corticosteroids, or corticosteroids are contraindicated in this patient; OR
       Note: Examples of corticosteroids are prednisone, methylprednisolone.
    2. The patient has tried one other agent for Crohn's disease; OR

Note: Examples of other agents for Crohn's disease include azathioprine, 6-mercaptopurine, or methotrexate (MTX). A previous trial of a biologic (e.g., Cimzia [certolizumab pegol SC injection], Entyvio [vedolizumab IV infusion], an infliximab product, or Stelara [ustekinumab IV infusion, ustekinumab SC injection] also counts as a trial of one other agent for Crohn's disease.

3. The patient has enterocutaneous (perianal or abdominal) or rectovaginal fistulas; OR

4. The patient has had ileocolonic resection (to reduce the chance of Crohn's disease recurrence); AND

iii. The agent is prescribed by or in consultation with a gastroenterologist.

B) Patients Currently Receiving an Adalimumab Product. 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 an adalimumab product.

F) Juvenile Idiopathic Arthritis (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. The patient meets ONE of the following conditions (a, b, c, or d):

a) The patient has tried one other agent for this condition; OR

Note: Examples of other agents for JIA include methotrexate (MTX), sulfasalazine, or leflunomide, a nonsteroidal anti-inflammatory drug (NSAID) [e.g., ibuprofen, naproxen]. A previous trial of a biologic (e.g., an etanercept product, an infliximab product, Actemra [tocilizumab IV infusion, tocilizumab SC injection], Kineret [anakinra SC injection], Orencia [abatacept IV infusion, abatacept SC injection]) also counts as a trial of one agent for JIA.

b) The patient will be starting on an adalimumab product 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 contraindications to MTX include pregnancy, breast feeding, alcoholic liver disease, immunodeficiency syndrome, 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 an Adalimumab Product. 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, 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 adalimumab product.

G) Hidradenitis Suppurativa. 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 patients meets BOTH of the following (i and ii):

i. The patient has tried at least ONE other therapy; AND

Note: Examples include intralesional or oral corticosteroids (such as triamcinolone, prednisone), systemic antibiotics (e.g., clindamycin, dicloxacillin, erythromycin), or isotretinoin).

ii. The agent is prescribed by or in consultation with a dermatologist.

B) Patients Currently Receiving an Adalimumab Product. 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 an adalimumab product.

H) 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. 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):

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 has a 3-month trial or previous intolerance to at least one biologic (e.g., Cimzia [certolizumab pegol SC injection], an etanercept product, an infliximab product, Cosentyx [secukinumab SC injection], Ilumya [tildrakizumab SC injection], Siliq [brodalumab SC injection], Stelara [ustekinumab SC injection], Skyrizi [risankizumab-rzaa SC injection], Taltz [ixekizumab SC injection], or Tremfya [guselkumab SC injection]). 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) 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) Patients Currently Receiving an Adalimumab Product. 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 an adalimumab product.

I) 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) Patients Currently Receiving an Adalimumab Product. 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; 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 an adalimumab product.

J) 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.** The patient is 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 had a trial of one systemic agent; OR
    Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone or methylprednisolone. A previous trial of a biologic (e.g., an infliximab product, Simponi SC [golimumab SC injection], or Entyvio [vedolizumab IV infusion]) also counts as a trial of one systemic agent for UC.
  - **b)** The patient has pouchitis AND 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 agent is prescribed by or in consultation with a gastroenterologist.

B) Patients Currently Receiving an Adalimumab Product. 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 an adalimumab product.

K) Uveitis (including other posterior uveitides and panuveitis 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 the following criteria (i and ii):
- **i.** The patient has tried ONE of the following therapies: periocular, intraocular, or systemic corticosteroids for this condition; AND
  Note: Examples of corticosteroids include prednisolone, triamcinolone, betamethasone, methylprednisolone, and prednisone. Examples of immunosuppressives include methotrexate (MTX), 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 had a trial of an etanercept or infliximab product for uveitis. These patients who have already tried a biologic for uveitis are not required to try a another agent.
- **ii.** The agent is prescribed by or in consultation with an ophthalmologist.

B) Patients Currently Receiving an Adalimumab Product. Approve for 3 years if the patient has 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, but there should have been a recent or past response to an adalimumab product.

Other Uses with Supportive Evidence

L) Behcet's Disease. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):

A) The patient meets BOTH of the following (i and ii):
- **i.** Initial Therapy. Approve for 3 months if the patient meets ONE of the following conditions (a or b):
  - **a)** The patient has tried at least ONE conventional therapy; OR
    Note: Examples include systemic corticosteroids (e.g., methylprednisolone), immunosuppressants (e.g., azathioprine, methotrexate [MTX], 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 etanercept or infliximab 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) The patient has ophthalmic manifestations of Behcet's disease; AND

ii. The agent is prescribed by or in consultation with a rheumatologist, dermatologist, ophthalmologist, gastroenterologist, or neurologist.

B) Patients Currently Receiving an Adalimumab Product. Approve for 1 year if the patient has responded to therapy, as determined by the prescriber.
Note: The patient may not have a full response, but there should a recent or past response to an adalimumab product.

M) Pyoderma Gangrenosum. 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 BOTH of the following (i and ii):

i. The patient meets ONE of the following conditions (a or b):

a) The patient has tried one systemic corticosteroid; OR
Note: An example is prednisone.

b) The 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.

ii. The agent is prescribed by or in consultation with a dermatologist.

B) Patients Currently Receiving an Adalimumab Product. Approve for 1 year if the patient has responded to therapy, as determined by the prescriber.
Note: The patient may not have a full response but there should be a recent or past response to an adalimumab product.

N) Sarcoidosis. 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 at least ONE corticosteroid for this condition; AND
Note: An example is prednisone.

ii. The patient has tried at least one immunosuppressive agent; AND
Note: Examples include methotrexate (MTX), leflunomide, azathioprine, mycophenolate mofetil, cyclosporine, Leukeran (chlorambucil), cyclophosphamide, Thalomid® (thalidomide capsules), an infliximab product, or chloroquine.

iii. The agent is prescribed by or in consultation with a pulmonologist, ophthalmologist, or dermatologist.

B) Patients Currently Receiving an Adalimumab Product. Approve for 1 year if the patient has responded to therapy, as determined by the prescriber.
Note: The patient may not have a full response but there should be a recent or past response to an adalimumab product.

O) 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 (i and ii):

i. The 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 IV corticosteroids (such as

prednisone, prednisolone, methylprednisolone); methotrexate (MTX); cyclosporine; or other immunosupressants.

ii. The agent is prescribed by or in consultation with an ophthalmologist.

B) Patients Currently Receiving an Adalimumab Product. Approve for 1 year if the patient has responded to therapy, 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 but there should be a recent or past response to an adalimumab product.

P) Spondyloarthritis, Other Subtypes (e.g., undifferentiated arthritis, non-radiographic axial aponyloarthritis, Reactive Arthritis [Reiter's disease], arthritis associated with inflammatory bowel disease [IBD]) [NOTE: For AS or PsA, refer to the respective criteria under FDA-approved indications]. 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. The patient meets one of the following conditions (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 disease-modifying antirheumatic drug (DMARD) has been tried; OR
Note: Examples include methotrexate [MTX], leflunomide, sulfasalazine.

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. The agent is prescribed by or in consultation with a rheumatologist.

B) Patients Currently Receiving an Adalimumab Product. 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, 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 adalimumab product.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Humira 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).** An adalimumab product 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.[15-16] Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with an adalimumab product.

2. **Polymyalgia Rheumatica (PMR).** EULAR/ACR guidelines for the management of PMR (2015) strongly recommend against the use of TNFis for treatment of PMR.[17] This recommendation is based on lack of evidence for benefit as well as considerable potential for potential harm.

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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OVERVIEW OF DISEASE STATE FOR PRIOR AUTHORIZATION DOCUMENT

Subject: Biologics for Ankylosing Spondylitis

Date Reviewed: March 29, 2016

Ankylosing spondylitis (AS) is part of a family of spondyloarthropathies which includes psoriatic arthritis (PsA), reactive arthritis, enteropathic arthritis, and undifferentiated spondyloarthropathy.[1-2] AS is a chronic, progressive, inflammatory disease that primarily affects the axial skeleton, peripheral joints, and entheses.[3] It usually occurs in late adolescence and early adulthood and disease progression is associated with pain, joint stiffness, and loss of spinal mobility that can result in severe functional disability.[1,3] Pain, fatigue, and stiffness are core components of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).[4] Another tool for assessment of disease activity is the AS Disease Activity Score (ASDAS). Components of the ASDAS include back pain, morning stiffness, patient global assessment of disease, pain and swelling in peripheral joints, and C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR). The ASDAS version with the CRP is preferred, though the ESR version may be used if the CRP is not available.[4-5] ASDAS versions with CRP and ESR are not interchangeable and the same version should be used consistently for a patient. Clinical measures such as joint tenderness and swelling, spinal motion, global and pain response measures, functional indices and acute phase reactants have been used and are also validated.[6] The goal of treatment is to reduce symptoms, maintain spinal flexibility and normal posture, reduce functional limitations, maintain ability to work, and decrease disease complications.[7]

Guidelines from the American College of Rheumatology (ACR) and the Spondyloarthritis Research and Treatment Network (SPARTAN) [2015] generally recommended TNFs for patients who have active disease despite treatment with an NSAID.[7] There is not a preference for TNF inhibitor, except for in the cases of concomitant inflammatory bowel disease or recurrent iritis, when a monoclonal antibody (e.g., Humira® [adalimumab for subcutaneous {SC} injection], Remicade [infliximab for intravenous infusion]) is recommended over Enbrel® (etanercept for SC injection). In patients with active AS despite use of a TNFi, an alternative TNFi is recommended over use of slow-acting antirheumatic drugs of non-TNFi biologics. If the patient has a contraindication to use of a TNFi, slow-acting antirheumatic drugs (e.g., methotrexate, sulfasalazine, leflunomide) are recommended over use of non-TNFi biologics. The guidelines strongly recommend against use of corticosteroids in patients with active disease. Of note, these guidelines were published prior to the approval of an interleukin (IL)-17 blocker (Cosentyx® [secukinumab for SC injection]) indicated for AS.

TNF antagonists modify the symptoms of AS but they are not DMARDs or disease controlling antirheumatic treatments for this condition.[8-9] Treatment goals include improving the signs and symptoms of AS, such as reduction of spinal pain and stiffness; control of peripheral arthritis, enthesitis, and dactylitis; and prevention of extra-articular disease manifestations (e.g., uveitis).[1]

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PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Arcalyst® (rilonacept for subcutaneous injection – Regeneron Pharmaceuticals)

DATE REVIEWED: 11/06/2019; selected revision 04/01/2020

OVERVIEW

Arcalyst is an interleukin-1 (IL-1) blocker indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children aged 12 years and older.[1] Arcalyst, also known is a recombinant dimeric fusion protein that blocks IL-1β signaling and to a lesser extent also binds IL-1α and IL-1 receptor antagonist (IL-1ra). In adults ≥ 18 years of age, Arcalyst is initiated with a loading dose of 320 mg delivered as two subcutaneous (SC) injections of 160 mg on the same day at two separate sites. Dosing is continued with 160 mg once weekly as a single injection. In adolescents aged 12 to 17 years, therapy is initiated with a loading dose of 4.4 mg/kg, up to a maximum of 320 mg, delivered as one or two SC injections with a maximum single-injection volume of 2 mL. If the initial dose is two injections, then patients should be given Arcalyst on the same day at two separate sites. In adolescents, dosing is continued with 2.2 mg/kg, up to a maximum of 160 mg, once weekly as a single injection.

Disease Overview

CAPS is a rare inherited inflammatory disease associated with overproduction of IL-1. CAPS encompasses three rare genetic syndromes. FCAS, MWS, and neonatal onset multisystem inflammatory disorder (NOMID) or chronic infantile neurological cutaneous and articular syndrome (CINCA) are thought to be one condition along a spectrum of disease severity.[2-3] FCAS is the mildest phenotype and NOMID is the most severe. There are no reliable prevalence statistics for CAPS, but the estimated number of persons with CAPS in the US is 200 to 500. These three disorders may be associated with mutations in the *CIAS-1* gene and have autosomal dominant inheritance. Mutations in the *CIAS-1* gene, which encodes a protein (cryopyrin), cause excess release of IL-1β and an inflammatory response. IL-1 cytokine signaling is important in the pathogenesis of CAPS. These autoinflammatory syndromes are caused by episodes of inflammation and are distinct from autoimmune disorders. The inflammatory symptoms in these patients include atypical urticaria, rash that is worse in the evening, fever, chills, fatigue, arthralgia, and conjunctival erythema. Exacerbations or flares can be triggered by exposure to cold, stress, exercise, or other stimuli. Patients with NOMID may have sensorineural hearing impairment, increased intracranial pressure, and

joint abnormalities. One-fourth of patients with MWS may develop systemic amyloid A (AA) amyloidosis which usually presents with renal impairment and nephrotic syndrome; amyloidosis is less common in the other forms of CAPS.

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 (CAPS) (including Familial Cold Autoinflammatory Syndrome [FCAS], Muckle-Wells Syndrome [MWS], 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):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets the following conditions (i and ii):
     - **i.** The patient is ≥ 12 years of age; AND
     - **ii.** Arcalyst 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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Arcalyst 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.)

176. **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 TNF blocking agents. An increased incidence of serious infections has been associated with another IL-1 blocker (Kineret) when given in combination with TNF antagonists.

177. **COVID-19 (Coronavirus Disease 2019).** Forward all requests to the Medical Director.
   Note: This includes requests for cytokine release syndrome associated with COVID-19.

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

1. Arcalyst® for injection [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals Inc; September 2016.
2. Shinkai K, McCalmont TH, Leslie KS. Cryopyrin-associated periodic syndromes and autoinflammation. *Clin Exp Dermatol.* 2008;33:1-9.
3. Ozen S, Hoffman HM, Frenkel J, et al. Familial Mediterranean Fever (FMF) and beyond: a new horizon. Fourth International Congress on the Systemic Autoinflammatory Diseases held in Bethesda, USA, 6-10 November 2005. *Ann Rheum Dis.* 2006;65:961-964.

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Benlysta® (belimumab intravenous injection – Human Genome Sciences, Inc./GlaxoSmithKline)

DATE REVIEWED: 05/27/2020

OVERVIEW

Benlysta intravenous is a B-lymphocyte stimulator (BLyS)-specific inhibitor.[1] It is indicated for the treatment of active, autoantibody-positive, systemic lupus erythematosus (SLE) in patients ≥ 5 years of age who are receiving standard therapy. Benlysta intravenous has not been studied and is not recommended in those with severe active lupus nephritis, severe active central nervous system (CNS) lupus, or in combination with other biologics or intravenous (IV) cyclophosphamide. 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

Guidelines from the European League Against Rheumatism (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. Guidelines for lupus nephritis from the American College of Rheumatology (ACR) [2012] do not address Benlysta's place in therapy.[3]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Benlysta intravenous. 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. Approvals are authorized 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 Benlysta IV is recommended in those who meet the following criteria:

FDA-Approved Indications

A) Systemic Lupus Erythematosus (SLE). Approve for the duration noted if the patient meets ONE of the following (A or B):
- **C)** Initial Therapy. Approve for 4 months if the patient meets ALL of the following conditions (i, ii, iii, and iv):
  - **i.** The patient is ≥ 5 years of age; AND
  - **ii.** The 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.** The patient meets ONE of the following (a or b):
    - **a)** The agent 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)** The patient is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber; AND
  - **iv.** The agent is prescribed by or in consultation with 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.** The patient meets ONE of the following (a or b):
    - **a)** The agent 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)** The patient is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber; AND
  - **ii.** The agent is prescribed by or in consultation with rheumatologist, clinical immunologist, nephrologist, neurologist, or dermatologist; AND
  - **iii.** The 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
Benlysta Intravenous 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.)

179. **Concurrent Use with Other Biologics or with Cyclophosphamide Intravenous (IV).** Benlysta SC has not been studied and is not recommended in combination with other biologics or intravenous (IV) cyclophosphamide in patients with SLE.[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.

180. **Rheumatoid Arthritis (RA).** A Phase II dose-ranging study evaluating patients with RA 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 RA.

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

1. Benlysta® injection [prescribing information]. Rockville, MD: Human Genmome Science Inc./GlaxoSmithKline; January 2020.
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.

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 – Benlysta® (belimumab subcutaneous injection – Human Genome Sciences, Inc./GlaxoSmithKline)

DATE REVIEWED: 05/27/2020

OVERVIEW

Benlysta subcutaneous (SC) is a B-lymphocyte stimulator (BLyS)-specific inhibitor.[1] It is indicated for the treatment of active, autoantibody-positive, systemic lupus erythematosus (SLE) in adults who are receiving

standard therapy. Benlysta SC has not been studied and is not recommended in those with severe active lupus nephritis, severe active central nervous system (CNS) lupus, or in combination with other biologics or intravenous (IV) cyclophosphamide. In some of the clinical trials with Benlysta IV, Black patients had a lower response rate for the primary endpoint relative to Black patients receiving placebo; therefore, caution is recommended when considering Benlysta SC in Black patients. Benlysta SC is given as a 200 mg SC injection once weekly (QW) in the abdomen or thigh. Patients transitioning from Benlysta intravenous (IV) should receive the first SC dose 1 to 4 weeks after the last IV dose. Benlysta SC has not been evaluated and is not available in a syringe for pediatric use. However, Benlysta IV is indicated in patients ≥ 5 years of age.

Guidelines

Guidelines from the European League Against Rheumatism (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. Guidelines for lupus nephritis from the American College of Rheumatology (ACR) [2012] do not address Benlysta's place in therapy.[3]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Benlysta SC. Because of the specialized skills required for evaluation and diagnosis of patients treated with Benlysta SC as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Benlysta SC 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 SC is recommended in those who meet the following criteria:

FDA-Approved Indications

B) Systemic Lupus Erythematosus (SLE). Approve Benlysta SC 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 ALL of the following criteria (i, ii, iii, and iv):
  - **iv.** The patient is an adult ≥ 18 years of age; AND
  - **v.** The 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.
  - **vi.** The patient meets ONE of the following (a or b):
    - **a)** The agent 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) The patient is determined to be intolerant standard therapy due to a significant toxicity, as determined by the prescriber; AND

vii. The agent is prescribed by or in consultation with rheumatologist, clinical immunologist, nephrologist, neurologist, or dermatologist.

C) Patient is Currently Receiving Benlysta Subcutaneous or Intravenous. Approve for 3 years if the patient meets ALL of the following criteria (i, ii, and iii):

i. The patient meets ONE of the following (a or b):

a) The agent 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) The patient is determined to be intolerant due to a significant toxicity, as determined by the prescriber; AND

ii. The agent is prescribed by or in consultation with rheumatologist, clinical immunologist, nephrologist, neurologist, or dermatologist; AND

iii. The 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

Benlysta 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.)

182. Concurrent Use with Other Biologics or with Cyclophosphamide Intravenous (IV). Benlysta SC has not been studied and is not recommended in combination with other biologics or intravenous (IV) cyclophosphamide in patients with SLE.[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.

183. Rheumatoid Arthritis (RA). A Phase II dose-ranging study evaluating patients with RA 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 RA.

184. 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.

APPENDIX

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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 – Cimzia® (certolizumab pegol for subcutaneous injection [lyophilized powder or solution] – UCB)

REVIEW DATE: 04/22/2020

OVERVIEW

Cimzia, a tumor necrosis factor inhibitor (TNFi), is a recombinant humanized antibody Fab´ fragment (fragment antigen binding) that is a covalent conjugate to polyethylene glycol (PEG).[1] Pegylation delays

the elimination of PEG polymers and the antibody, thus increasing the terminal elimination half-life of the Fab fragment. Unlike infliximab and adalimumab, Cimzia does not contain an Fc portion of the antibody.

Cimzia is indicated for the following uses:[1]

1. 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; AND
2. Rheumatoid arthritis (RA), for the treatment of adults with moderately to severely active disease; AND
3. Psoriatic arthritis (PsA), for the treatment of adult patients with active disease; AND
4. Ankylosing spondylitis, for the treatment of adults with active disease; AND
5. Plaque psoriasis, for the treatment of adults with moderately to severely active disease who are candidates for systemic therapy or phototherapy; AND
6. Non-radiographic axial spondyloarthritis (nr-axSpA), in patients with objective signs of inflammation.

Cimzia may be used as monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).

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 Crohn's 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. Cimzia 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.
- Crohn's Disease: The American College of Gastroenterology (ACG) 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 (AAD) and National Psoriasis Foundation (NPF) recommend adalimumab as a monotherapy treatment option for adults with moderate to severe disease.[4]
- 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]

Safety

Cimzia has Boxed Warnings concerning risks of serious infection and the risk of malignancy.[1] Prior to initiating therapy with Cimzia, 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 Cimzia; if a serious infection or sepsis develops, Cimzia should be discontinued. Lymphoma and other malignancies have been reported in patients who have taken TNFis such as Cimzia.

Other Uses with Supportive Evidence

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 (AEs) 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 (AS).** Approve Cimzia for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if Cimzia is prescribed by or in consultation with a rheumatologist.
   - **B)** Patients Currently Receiving Cimzia. 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 Cimzia.

2. **Crohn's Disease.** Approve Cimzia 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.** 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 or is currently taking corticosteroids, or corticosteroids are contraindicated in this patient; OR
       - **b)** The patient has tried one other systemic agent for Crohn's disease.
         Note: Examples of systemic therapies for Crohn's disease include azathioprine, 6-mercaptopurine, and methotrexate (MTX). 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; AND

iii. Cimzia is prescribed by or in consultation with a gastroenterologist.

B) Patients Currently Receiving Cimzia. 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 Cimzia. 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.

3. Non-Radiographic Axial Spondyloarthritis (nr-axSpA). 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. The 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. Cimzia is prescribed by or in consultation with a rheumatologist.

B) Patients Currently Receiving Cimzia. 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 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 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 has 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

b) The patient has a contraindication to methotrexate (MTX), as determined by the prescriber; AND

iii. Cimzia is prescribed by or in consultation with a dermatologist.

B) Patients Currently Receiving Cimzia. 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 Cimzia.

5. Psoriatic Arthritis (PsA). Approve Cimzia for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if Cimzia is prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patients Currently Receiving Cimzia. 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; improvements in acute phase reactants (for example, CRP). The patient may not have a full response, but there should have been a recent or past response to Cimzia.

6. Rheumatoid Arthritis (RA). Approve Cimzia 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 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. Cimzia is prescribed by or in consultation with a rheumatologist.

B) Patients Currently Receiving Cimzia. 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 Cimzia.

Other Uses with Supportive Evidence

7. Spondyloarthritis (SpA), Other Subtypes (e.g., undifferentiated arthritis, reactive arthritis [Reiter's disease]) [NOTE: For ankylosing spondylitis, psoriatic arthritis, or non-radiographic axial spondyloarthrits, refer to the respective criteria under FDA-approved indications]. 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 ALL of the following conditions (i, ii, and iii):

i. The patient has arthritis primarily in the knees, ankles, elbows, wrists, hands, and/or feet; AND

ii. The patient has tried at least ONE conventional synthetic disease-modifying antirheumatic drug (DMARD).

Note: Examples include methotrexate (MTX), leflunomide, and sulfasalazine; AND

iii. Cimzia is prescribed by or in consultation with a rheumatologist.

B) Patients Currently Receiving Cimzia. 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, 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

Cimzia 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.)

4. **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., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Cimzia.

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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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 – 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

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 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.

R) 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.

S) 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.

T) 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.

185. **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]

186. **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]

187. **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]

188. 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]

189. 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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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):
   D) 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.
   E) 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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PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Etanercept Products
- Enbrel® (etanercept for subcutaneous injection – Immunex/Amgen)

REVIEW DATE: 11/06/2019

OVERVIEW

Etanercept products are human soluble receptor fusion proteins which inhibit the binding of tumor necrosis factor (TNF)α and β to cell surface TNF receptors.[1] TNF is a proinflammatory cytokine that is involved in normal inflammatory and immune responses. At this time, Enbrel is the only etanercept product commercially available in the US. Enbrel is indicated for the following uses:

1. Rheumatoid arthritis, 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; AND
2. Juvenile idiopathic arthritis (JIA), for reducing the signs and symptoms of moderate or severe active polyarticular disease in patients aged ≥ 2 years; AND
3. Psoriatic arthritis (PsA), for reducing the signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis (PsA); AND
4. Ankylosing spondylitis (AS), for reducing signs and symptoms in patients with active disease; AND
5. 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.

For RA and PsA, Enbrel can be used in combination with methotrexate (MTX) or used alone.[1]

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 psoriasis, psoriatic arthritis, and rheumatoid arthritis (RA). Increased levels of TNF are found in the

synovial fluid of patients with RA, JIA, AS, and PsA; TNF has an important role in both the pathologic inflammation and the joint destruction that are characteristic of this disease. In psoriasis, increased levels of TNF are found in the blood and skin lesions. Etanercept products neutralize the biological activity of TNFα and inhibits binding of TNFα with its receptors.

Guidelines

TNFis feature prominently in guidelines for treatment of inflammatory conditions.

- 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).[2]
- Juvenile Idiopathic Arthritis: In polyarticular disease, the 2019 ACR recommendations propose initial DMARD treatment with a conventional synthetic DMARD such as MTX in most patients prior to a TNFi.[3] In those who are secondary nonresponders to a TNFi, a second TNFi may be tried; however, a non-TNF biologic is recommended for primary nonresponders. TNFis may also be used as second- or third-line treatment for systemic JIA.[4]
- 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.
- Plaque Psoriasis: Guidelines from the American Academy of Dermatologists (AAD) and National Psoriasis Foundation (NPF) [2019] recommend adalimumab 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 PsA and in those who were previously treated with an oral therapy.[7]
- Ocular Inflammatory Disorders: The American Academy of Ophthalmology (AAO) [2014] note that TNFis 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 MTX has failed or is not tolerated and may be used as corticosteroid-sparing treatment for vision-threatening chronic uveitis from seronegative spondyloarthropathy. 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).
- Behcet's Disease: 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 AAO 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]
- Pyoderma Gangrenosum: Although guidelines are not current, multiple topical and systemic therapies have been used for pyoderma gangrenosum.[10-13] Oral prednisone is the most common initial immunosuppressant medication. Other systemic therapies include cyclosporine, MTX, azathioprine, cyclophosphamide, mycophenolate mofetil, and TNFis (infliximab, etanercept, adalimumab). In case reports, TNFis have been effective.
- Graft versus Host Disease: Guidelines (2012) generally recommend TNFis as a treatment option following a trial of first-line agent(s) [e.g., cyclosporine, intravenous methylprednisolone] for acute GVHD (grade III or IV disease).[14-15] A number of small studies demonstrate efficacy when etanercept was used in GVHD.[16-23]

- 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.

Safety
Etanercept products have 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; periodically during therapy, patients should be assessed for latent TB infection. Patients should also be monitored for signs and symptoms of infection during and after treatment with an etanercept product, and if a serious infection or sepsis develops, discontinue therapy. It is also noted that lymphoma and other malignancies have been reported in children and adolescents taking TNFis.

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 (AEs) 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. **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.** The patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months.
       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 (e.g., Cimzia [certolizumab pegol SC injection], an adalimumab product, an infliximab product, Simponi [golimumab SC injection], Simponi Aria [golimumab IV infusion], Actemra [tocilizumab IV infusion; tocilizumab SC injection], Kevzara [sarilumab SC injection], Kineret [anakinra SC injection], Orencia [abatacept IV infusion; abatacept SC injection], or a rituximab product). 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 an Etanercept Product. 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 an etanercept product.

2. **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) Patients Currently Receiving an Etanercept Product. 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, or improvement in 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 etanercept product.

3. **Juvenile Idiopathic Arthritis (JIA) [or Juvenile Rheumatoid Arthritis {JRA}] (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):
   U) Initial Therapy. Approve 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):
         i) The patient has tried one other agent for this condition.
         Note: Examples of other agents for JIA include methotrexate (MTX), sulfasalazine, or leflunomide, a nonsteroidal anti-inflammatory drug (NSAID) [e.g., ibuprofen, naproxen]. A previous trial of a biologic (e.g., an adalimumab product, an infliximab product, Actemra [tocilizumab IV infusion, tocilizumab SC injection], Kineret [anakinra SC injection], or Orencia [abatacept IV infusion, abatacept SC injection]) also counts as a trial of one agent for JIA; OR
         j) The patient will be starting on an etanercept product concurrently with methotrexate (MTX), sulfasalazine, or leflunomide; OR
         k) The patient has an absolute contraindication to methotrexate (MTX), sulfasalazine, or leflunomide.
         Note: Examples of contraindications to MTX include pregnancy, breast feeding, alcoholic liver disease, immunodeficiency syndrome, blood dyscrasias; OR
         l) 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 an Etanercept Product. 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, 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 etanercept product.

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 criteria (i, ii, and iii):
      i. The patient is greater than or equal to 4 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 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 has a 3-month trial or previous intolerance to at least one biologic (e.g., an adalimumab product, Cimzia [certolizumab pegol SC injection], an infliximab product, Siliq [brodalumab SC injection], Cosentyx® [secukinumab SC injection], Ilumya

[tildrakizumab SC injection], Stelara® [ustekinumab SC injection], Skyrizi [risankizumab-rzaa SC injection], Taltz® [ixekizumab SC injection], or Tremfya [guselkumab SC injection]). 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. The agent is prescribed by or in consultation with a dermatologist.

B) Patients Currently Receiving an Etanercept Product. 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 an etanercept product.

5. Psoriatic Arthritis (PsA). 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) Patients Currently Receiving an Etanercept Product. 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; 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 an etanercept product.

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. The patient has tried at least one conventional therapy.
Note: Examples include systemic corticosteroids (e.g., methylprednisolone), immunosuppressants (e.g., azathioprine, methotrexate [MTX], 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. These patients who have already tried a biologic for Behcet's disease are not required to "step back" and try a conventional therapy); OR

ii. The agent is prescribed by or in consultation with a rheumatologist, dermatologist, ophthalmologist, gastroenterologist, or neurologist.

B) Patients Currently Receiving an Etanercept Product. Approve for 1 year if the patient has responded to therapy, as determined by the prescriber.
Note: The patient may not have a full response, but there should a recent or past response to an etanercept product.

7. Graft-Versus-Host Disease (GVHD). 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 ONE of the following (i or ii):

i. The patient meets one of the following conditions (i or ii):

a) The Patient has tried one conventional treatment for graft-versus-host disease (GVHD) [e.g., high-dose systemic corticosteroids, antithymocyte globulin, cyclosporine, thalidomide, tacrolimus, mycophenolate mofetil]; OR

b) The patient is concurrently receiving at least one of these medications (e.g., high-dose systemic corticosteroids, antithymocyte globulin, cyclosporine, Thalomid® (thalidomide capsules), tacrolimus, mycophenolate mofetil) in combination with an etanercept product.

Note: Examples of conventional treatments the patient may have tried or may be receiving include a high-dose corticosteroid (e.g., methylprednisolone), antithymocyte globulin, cyclosporine, Thalomid (thalidomide tablets), tacrolimus, and mycophenolate mofetil; AND

ii. The agent is prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center.

B) Patients Currently Receiving an Etanercept Product. Approve for 3 months if the patient has responded to therapy, 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 criteria (i and ii):

14 The patient meets ONE of the following (a or b):

a) The patient has tried one systemic corticosteroid; OR

b) The patient has tried one other immunosuppressant for at least 2 months or was intolerant to one of these agents;

Note: Examples include mycophenolate mofetil and cyclospore; AND

15 The agent is prescribed by or in consultation with a dermatologist.

B) Patients Currently Receiving an Etanercept Product. Approve for 1 year if the patient has responded to therapy, as determined by the prescriber.

Note: There may not have been a full response, but there should a recent or past response to an etanercept product.

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 The patient has tried one other therapy for these.

Note: Examples include oral nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin, naproxen, or ibuprofen; oral, topical (ophthalmic) or IV corticosteroids (such as prednisone, prednisolone, methylprednisolone); methotrexate (MTX); cyclosporine; or other immunosupressants; AND

15 The agent is prescribed by or in consultation with an ophthalmologist.

B) Patients Currently Receiving an Etanercept Product. Approve for 1 year if the patient has responded to therapy, 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 but there should be a recent or past response to an etanercept product.

10. 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 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 meets ONE of the following conditions (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 disease-modifying antirheumatic drug (DMARD) has been tried.
Note: Examples include methotrexate [MTX], leflunomide, 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)]:
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 agent is prescribed by or in consultation with a rheumatologist.

D) Patients Currently Receiving an Etanercept Product. 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, 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 etanercept product.

11. Still's Disease (systemic-onset RA in adults, the disease may have begun in childhood). 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 to a conventional synthetic DMARD.
Note: An example is methotrexate; AND
16 The agent is prescribed by or in consultation with a rheumatologist.

B) Patients Currently Receiving an Etanercept Product. Approve for 1 year if the patient has responded to therapy, 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 an etanercept product.

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.
Note: Examples of corticosteroids include prednisolone, triamcinolone, betamethasone, methylprednisolone, and prednisone. Examples of immunosuppressives include methotrexate (MTX), 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 had a trial of an adalimumab or infliximab product for uveitis. These patients who have already tried a biologic for uveitis are not required to try a another agent; AND
15 The agent is prescribed by or in consultation with an ophthalmologist.

B) Patients Currently Receiving an Etanercept Product. Approve for 1 year if the patient has responded to therapy, 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, but there should have been a recent or past response to an etanercept product.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Etanercept products (Enbrel) 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. **Concurrent Use with a Biologic DMARD or Targeted Synthetic 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., MTX, 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 (MTX, 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 Remicade or Humira may be considered as second-line immunomodulary 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 MTX 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 Humira and Remicade 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, 50% of etanercept patients and 22.2% of placebo patients were able to control the disease without corticosteroid therapy (not statistically significant). But 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 Remicade (n = 21) or etanercept (n = 9).[44] Five patients who were initially treated with etanercept were switched to Remicade. Therapy with anti-TNF agents 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, MTX, 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 AE 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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APPENDIX

Brand (generic name)	Mechanism of Action
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6
Kevzara® (sarilumab SC injection)	Inhibition of IL-6
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator
Rituximab IV Products (Rituxan®, biosimiars)	CD20-directed cytolytic antibody
Kineret® (anakinra SC injection)	Inhibition of IL-1
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23
Siliq™ (brodalumab SC injection)	Inhibition of IL-17
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist
Otezla® (apremilast tablets)	Inhibition of PDE4
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways

SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase.

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

2. **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):
   3. 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.
   4. Patient is Currently Receiving Ilaris. Approve for 1 year if the patient has had a response, as determined by the prescriber.

5. **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 1 year 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 1 year 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 1 year 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 1 year 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 1 year 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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PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Ilumya™ (tildrakizumab-asmn for subcutaneous injection – Sun Pharmaceuticals)

REVIEW DATE: 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:

V) 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.)

190. 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.

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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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.

OVERVIEW OF DISEASE STATE FOR PRIOR AUTHORIZATION DOCUMENT

Subject: Biologics for Inflammatory Bowel Disease

Date Revised: 03/30/2017

INDICATIONS

Table 1. Products Approved for IBD.[*1-6]

	Cimzia	Entyvio	adalimumab products[#]	infliximab products[+]	Simponi SC	Stelara IV/SC	Tysabri
Crohn's Disease	√	√	√	√	--	√	√
Ulcerative Colitis	--	√	√	√	√	--	--

IBD – Inflammatory bowel disease; [*] Refer to the selected *ESI Standard Prior Authorization Policies* for the specific patient population approved for each indication; [#] Examples of adalimumab products include Amjevita and Humira; [+] Examples of infliximab products include Inflectra and Remicade; SC – Subcutaneous; IV – Intravenous.

CROHN'S DISEASE

Crohn's disease is characterized by inflammation in the gastrointestinal (GI) tract at any point from the mouth to the rectum.[7] In the US, the prevalence is 201 cases per 100,000 adults with the median age at diagnosis of 20 to 30 years of age. Though the cause of Crohn's disease is unknown, smoking and use of oral contraceptives and nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to exacerbate symptoms. Common symptoms include abdominal pain, diarrhea, fever, GI bleeding, and weight loss. It is common for patients to experience extra-intestinal manifestations such as anemia, ophthalmic manifestations (uveitis, episcleritis, scleritis) cholelithiasis, inflammatory arthropathies, osteoporosis, or venous thromboembolism. The goals of therapy include steroid-free sustained clinical remission, induction and maintenance of mucosal healing, potential induction and maintenance of radiological healing, prevention of surgery, maintenance of normal GI function, and prevention of disability.[8] To achieve these goals, the underlying inflammation must be treated rather than a treatment regimen that only treats symptoms. In Crohn's disease, surgery is not curative because disease recurs at the anastomotic site.

In clinical trials of Crohn's disease, the Crohn's Disease Activity Index (CDAI) is the most commonly used disease activity index.[9] The CDAI is a composite score that includes eight subjective and objective criteria: the number of liquid or very soft stools per day, the severity of abdominal pain or cramping, general well-being, the presence or absence of extra intestinal manifestations of disease, the presence or absence of an abdominal mass, the use of antidiarrheal agents, hematocrit and body weight. A higher score indicates more severe disease; the maximum score is 600 and > 450 indicates severe illness. Remission is usually defined as a CDAI of ≤ 150, and response is defined as a reduction in total score of between 70 and 100 points. Moderate-severe Crohn's disease (CDAI usually 220 to 450) refers to patients who have failed to respond to treatment for mild-moderate disease (CDAI usually 150 to 220) or those with more prominent symptoms of fevers, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia.[10] Therapy first treats acute disease or induces clinical remission and then maintains response/remission. Remission refers to patients who are asymptomatic or without inflammatory sequelae and includes patients who have responded to acute medical intervention or have undergone surgical resection without gross evidence of residual disease.

Practice Parameters for Crohn's Disease and Inflammatory Bowel Disease (IBD)

Guidelines for Crohn's disease have not been updated since the approval of adalimuamb for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease, whereas previously only infliximab was approved in patients ≤ 6 years of age with Crohn's disease.[1,4] Entyvio™ (vedolizumab injection for intravenous [IV] use) is an integrin receptor antagonist that has also been approved since the guidelines were published.[5] Entyvio is indicated for achieving a clinical response, achieving clinical remission, and achieving corticosteroid-free remission in adult patients with moderately to severely active CD who have had an

inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on steroids. Stelara is also been approved for treatment of moderately to severely active CD, in adults who have failed or were intolerant to immunomodulators or corticosteroids but not TNFis, or failed or were intolerant to at least one TNFi. Induction therapy is with a single weight-based infusion of Stelara IV administered by a healthcare professional followed by Stelara subcutaneous (SC) 90 mg injection 8 weeks later, then every 8 weeks thereafter for maintenance.

For CD in adults, the American Gastroenterological Association (AGA) has developed guidelines (2013) prior to the availability of Entyvio.[11] For induction therapy, TNF blockers are listed as a strong recommendation for patients with moderately severe CD (moderate-quality evidence). This compares with the recommendation *against* using thiopurine monotherapy to induce remission in patients with moderately severe CD (weak recommendation, moderate-quality evidence). However, starting a thiopurine at the same time as corticosteroids in a patient with moderately severe CD is noted to be a reasonable treatment strategy (strength of recommendation not provided). For induction, TNF blockers + thiopurines are recommended over thiopurine monotherapy in patients with moderately severe CD (strong recommendation, high-quality evidence). For induction, TNF blockers + thiopurines are recommended over TNF blocker monotherapy in patients with moderately severe CD (weak recommendation, moderate-quality evidence).

The AGA guidelines for CD do not mention Tysabri, an integrin receptor antagonist indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active CD with evidence of inflammation who have had an inadequate response to or are unable to tolerate conventional therapies and TNF blockers.[11] Of note, due to the risks of PML, Tysabri is only available through a restricted distribution program called the CD TOUCH® prescribing program.

ULCERATIVE COLITIS

Ulcerative colitis (UC) is a chronic condition resulting in inflammation of the colon.[12] In UC, there is always involvement of the rectum with inflammation spreading from the distal to the proximal colon. Though there is considerable variability among patients, typical symptoms of UC include abdominal pain, bloody and/or mucous diarrhea; severe cases may also present with weight loss, tachycardia, fever, anemia, and bowel distention. The goal of therapy is the rapid induction of a steroid-free remission and prevention of complications due to treatment of the disease. UC is curable by colectomy, and treatment algorithms generally favor a step-up approach, with Remicade, cyclosporine, tacrolimus, or surgery considered as rescue therapy.

Practice Guideline for Ulcerative Colitis

American College of Gastroenterology (ACG) practice guidelines for ulcerative colitis were published in 2010, prior to the approval of Entyvio, Humira, and Simponi® (golimumab for SC injection) in UC.[1-2,5] Remicade is recommended for mild-to-moderate extensive colitis (active disease) and has been effective in patients who are refractory to steroids or who are dependent on steroids despite adequate doses of a thiopurine (e.g., azathioprine, 6-mercaptopurine) or in patients who cannot tolerate these medications.[4] To maintain remission in mild to moderate extensive colitis, Remicade has been effective in patients who responded to induction therapy with Remicade. In patients with severe colitis who are refractory to optimized therapy with oral agents (prednisone, aminosalicylates) and topical agents, Remicade may be used if urgent hospitalization is not required.[4] Remicade may also be effective in helping to avoid colectomy in patients who fail on IV corticosteroids, but long term efficacy is not known. An evidence-based systematic review on medical therapies for IBD, including ulcerative colitis (2011) recommends mesalamine, steroids, or Remicade to induce remission in various patient populations.[13] In certain patients who are hospitalized with severe disease, IV cyclosporine may be considered. In patients who are in remission, mesalamine, azathioprine, or 6-mercaptopurine is recommended to prevent relapse. The review notes that there is insufficient evidence to make a recommendation for biologic agents and antibiotics to prevent relapse.

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PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Infliximab Products

- Avsola™ (infliximab-axxq for injection, for intravenous use – Amgen)
- Inflectra™ (infliximab-dyyb for injection, for intravenous use – Hospira/Pfizer)
- Remicade® (infliximab for intravenous infusion – Janssen Biotech, Inc.)
- Renflexis® (infliximab-abda intravenous infusion – Samsung Bioepis/Merck)

REVIEW DATE: 08/28/2019; selected revision 06/03/2020

OVERVIEW

Infliximab products are tumor necrosis factor inhibitors (TNFis) approved for the following indications:[1-3]

- **Rheumatoid arthritis** (RA), in combination with methotrexate (MTX) for reducing signs and symptoms, inhibiting the progression of structural damage and improving physical function in patients with moderately to severely active RA.
- **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 in the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adults with fistulizing Crohn's disease.
- **Ankylosing spondylitis** (AS), for reducing signs and symptoms of active disease;
- **Psoriatic arthritis** (PsA), for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage and improving physical function.
- **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; AND
- **Ulcerative colitis** (UC), for the following uses:
  - for 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
  - for reducing signs and symptoms and inducing and maintaining clinical remission 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). The recommended dose of infliximab is weight-based and varies slightly by indication. Dosing increase, interval shortening, or changing to another therapy is generally recommended for attenuation of response.[2]

Guidelines

TNFis feature prominently in guidelines for treatment of many inflammatory conditions.

- **Spondyloarthritis:** Guidelines from the Assessment of SpondyloArthritis International Society (ASAS)/EULAR (2016) recommend biologics (e.g., TNFis, Cosentyx) in patients with persistently high disease activity despite traditional conventional treatments (e.g., nonpharmacological management, NSAIDs).[4] Purely axial disease should not be treated with conventional synthetic DMARDs. Guidelines from the American College of Rheumatology (ACR) and the Spondyloarthritis Research and Treatment Network (SPARTAN) [2015] recommend TNFis for

patients with active disease despite treatment with an NSAID (includes patients with non-radiographic axial [nr-ax]SpA).[5] Predominantly axial manifestations are not recommended for a conventional synthetic DMARD prior to a TNFi. However, for symptomatic peripheral arthritis, a conventional synthetic DMARD is recommended (preferably sulfasalazine).

- **Crohn's Disease:** The American College of Gastroenterology (ACG) has guidelines for Crohn's disease (2018).[6] 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) recommend infliximab 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 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).[9]
- **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).[10] 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). A retrospective, open-label, case series demonstrated some efficacy of Humira in patients with pouchitis previously treated with infliximab.[10]

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:** 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:** In retrospective analyses and case series, infliximab has been effective in treating some patients with steroid-refractory acute or chronic graft-versus-host disease.[19-24] In a prospective study in 19 patients, infliximab was not effective in the *prophylaxis* of acute GVHD, but may have delayed platelet engraftment and was associated with frequent infectious complications. In studies evaluating the role of infliximab for treatment of steroid-refractory acute GVHD, the overall response rates ranged from 15% to 100%, with the highest response rates in patients with GI and skin disease.
- **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, JIA-associated uveitis, and other posterior uveitides and panuveitis syndromes).[13] Infliximab should be considered second-line in vision-threatening JIA-associated uveitis when MTX 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 in partnership with the American Society of Clinical Oncology (ASCO) [version 1.2019 – November 14, 2018] for Management of Immunotherapy-Related Toxicities.[14] Recommended therapies include use of infliximab to manage many toxicities. 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 2011 ACR recommendations for the treatment of JIA propose initial DMARD treatment with MTX in most patients; however, sulfasalazine is recommended for patients with enthesitis-related arthritis and may also be used in certain patients with sacroiliac arthritis.[15] Leflunomide may be an appropriate initial DMARD in those with high disease activity and/or a poor prognosis. Kineret may be used in systemic arthritis and Actemra may be used in systemic and polyarticular juvenile arthritis.[15-16] TNF antagonists such as infliximab may also be used as second- or third-line treatment for systemic JIA.[15]
- **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, MTX, 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, MTX, 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., MTX, azathioprine, leflunomide). If these agents fail or cause toxicity, adalimumab, infliximab, cyclophosphamide, or mycophenolate mofetil are proposed.

Dosing Information

The recommended dose of infliximab is weight-based and varies slightly by indication.[1-3] Dosing increase, interval shortening, or changing to another therapy is generally recommended for attenuation of response. Thus, published recommendations note that the dose and interval of infliximab may be adjusted, as needed, in patients who initially respond but then lose that response.[2] Additionally, data are emerging concerning tapering of infliximab dosage in patients with inflammatory conditions who are in remission or have low disease activity.[110-113] At this time, there is not a consensus regarding tapering. The 2015 ACR guidelines for RA mention tapering, defined as scaling back therapy (reducing dose or frequency) as a treatment option for patients who are in remission.[18] Although specific tapering schedules are not recommended, it is noted that minimizing therapy may decrease toxicity and lowers the risk of treating patients unnecessarily. When the dose of any RA therapy is tapered, it is recommended that there be a comprehensive plan to monitor disease activity and address possible flares.

Safety

Infliximab has Boxed Warnings concerning risks of serious infection and the risk of malignancy.[1] Prior to initiating therapy with infliximab, patients should be evaluated for active tuberculosis (TB) infection, and periodically during therapy patients should be assessed for latent TB infection. Patients should also be monitored for signs and symptoms of infection during and after treatment with infliximab, and if a serious infection or sepsis develops, infliximab should be discontinued. It is also recommended that patients treated with any TNF antagonist should be monitored for malignancies.

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 (AS).** 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)** Patients Currently Receiving an Infliximab Product. 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 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.** The patient is greater than or equal to 6 years of age; AND
     - **ii.** The patient meets ONE of the following conditions (a, b, c, or d):
       - **a)** The 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)** The patient has tried one other agent for Crohn's disease; OR
         Note: Examples of other agents for Crohn's disease include azathioprine, 6-mercaptopurine, or methotrexate (MTX). A previous trial of a biologic (e.g., Cimzia [certolizumab pegol SC injection], an adalimumab product [e.g., Humira], Entyvio [vedolizumab IV infusion], or Stelara [ustekizumab IV infusion, ustekizumab SC injection]) also counts as a trial of one other agent for Crohn's disease).
       - **c)** The patient has enterocutaneous (perianal or abdominal) or rectovaginal fistulas; OR
       - **d)** The patient has had ileocolonic resection (to reduce the chance of Crohn's disease recurrence); AND
     - **iii.** The agent is prescribed by or in consultation with a gastroenterologist.
   - **B)** Patients Currently Receiving an Infliximab Product. Approve for 1 year 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 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.** 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 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 has a 3-month trial or previous intolerance to at least one biologic (e.g., an adalimumab product [e.g., Humira], Cimzia [certolizumab pegol SC injection], an etanercept product [e.g., Enbrel], Cosentyx [secukinumab SC injection], Ilumya [tildrakizumab SC injection], Siliq [brodalumab SC injection], Skyrizi [risankizumab-rzaa SC injection], Stelara [ustekinumab for SC injection], Taltz [ixekizumab for SC injection), or Tremfya [guselkumab SC injection]). 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) The patient has a contraindication to methotrexate (MTX), as determined by the prescriber.

iii. The agent is prescribed by or in consultation with a dermatologist.

B) Patients Currently Receiving an Infliximab Product. Approve for 1 year 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 an infliximab product.

4. Psoriatic Arthritis (PsA). 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) Patients Currently Receiving an Infliximab Product. 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; 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 an infliximab product.

5. 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 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; 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 at least one biologic (e.g., Cimzia [certolizumab pegol SC injection], an etanercept product [e.g., Enbrel], an adalimumab product [e.g., Humira], Simponi/Aria [golimumab SC injection, golimumab IV infusion], Actemra [tocilizumab IV infusion, tocilizumab SC injection], Kevzara [sarilumab SC injection], Kineret [anakinra SC injection], Orencia [abatacept IV infusion, abatacept SC injection], and a rituximab product [Rituxan, Truxima]. These patients who have already tried a biologic for RA 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) Patients Currently Receiving an Infliximab Product. 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 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. The patient is greater than or equal to 6 years of age; AND

ii. The patient meets ONE of the following conditions (a or b):

a) Patient has 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 (e.g., an adalimumab product [e.g., Humira], Simponi SC [golimumab SC injection], or Entyvio [vedolizumab IV infusion] also counts as a trial of one systemic agent for UC).

b) The patient has pouchitis AND 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 agent is prescribed by or in consultation with a gastroenterologist.

B) Patients Currently Receiving an Infliximab Product. Approve for 1 year 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 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. The patient meets ONE of the following (a or b):

a) The patient has tried at least ONE conventional therapy; OR
Note: Examples include systemic corticosteroids (e.g., methylprednisolone), immunosuppressants (azathioprine, methotrexate [MTX], 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 [e.g., Humira], an etanercept product [e.g., Enbrel]). These patients who have already tried a biologic for Behcet's disease are not required to "step back" and try a conventional therapy).

b) The patient has ophthalmic manifestations of Behcet's disease; AND

ii. The agent is prescribed by or in consultation with a rheumatologist, dermatologist, ophthalmologist, gastroenterologist, or neurologist.

B) Patients Currently Receiving an Infliximab Product. Approve for 1 year if the patient has had a response, as determined by the prescriber.
Note: The patient may not have a full response by Month 2 or 3, but there should be some response.

8. Graft-Versus-Host Disease (GVHD). 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. The patient meets ONE of the following conditions (a or b):

a) Patient has tried one conventional treatment for graft-versus-host disease (GVHD); OR

b) Patient is concurrently receiving at least one of these medications in combination with an infliximab product; AND
Note: Examples of conventional treatments the patient may have tried or may be receiving include a high-dose corticosteroid (e.g., methylprednisolone), antithymocyte globulin, cyclosporine, Thalomid (thalidomide tablets), tacrolimus, and mycophenolate mofetil.

ii. The agent is prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center.

B) Patients Currently Receiving an Infliximab Product. Approve for 3 months if the has 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. The patient has tried one other therapy; AND
Note: Examples include intralesional or oral corticosteroids (such as triamcinolone, prednisone), systemic antibiotics (e.g., clindamycin, dicloxacillin, erythromycin), isotretinoin).

ii. The agent is prescribed by or in consultation with a dermatologist.

B) Patients Currently Receiving an Infliximab Product. Approve for 1 year if the patient has 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. The 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. The patient developed this immune-related toxicity while receiving a checkpoint inhibitor; AND
Note: Examples of checkpoint inhibitors include Keytruda (pembrolizumab IV infusion), Opdivo (nivolumab IV infusion), Yervoy (ipilimumab IV infusion), Tecentriq (atezolizumab IV infusion), Bavancio (avelumab IV infusion), or Imfinzi (durvalumab IV infusion).

iii. The patient has tried a systemic corticosteroid; AND
Note: Examples include methyprednisone and prednisone.

iv. The agent is prescribed by or in consultation with an oncologist, gastroenterologist, rheumatologist, or ophthalmologist.

D) Patients 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. The patient is greater than or equal to 6 years of age; AND

ii. Patient has tried one systemic corticosteroid; AND
Note: Examples include prednisone andmethylprednisolone.

iii. The patient has tried mesalamine; AND

iv. The patient has tried either azathioprine or 6-mercaptopurine; AND

v. The agent is prescribed by or in consultation with a gastroenterologist.

B) Patients Currently Receiving an Infliximab Product. Approve for 1 year if the patient has had a response, as determined by the prescriber.

12. Juvenile Idiopathic Arthritis (JIA) [or Juvenile Rheumatoid Arthritis {JRA}] (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 agent for this condition; OR
Note: Examples of other agents for JIA include methotrexate (MTX), sulfasalazine, or leflunomide, a nonsteroidal anti-inflammatory drug (NSAID) [e.g., ibuprofen, naproxen]. A previous trial of a biologic (e.g., an adalimumab product [e.g, Humira], an etanercept product [e.g., Enbrel], Orencia [abatacept IV infusion, abatacept SC injection], Kineret [anakinra SC injection], and Actemra [tocilizumab IV infusion, tocilizumab SC injection] also counts as a trial of one agent for JIA).

b) 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 an Infliximab Product. 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, 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. The patient meets ONE of the following conditions (a or b):

a) The patient has tried one systemic corticosteroid; OR
Note: An example is prednisone.

b) The 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.

ii. The agent is prescribed by or in consultation with a dermatologist.

B) Patients Currently Receiving an Infliximab Product. Approve for 1 year if the patient has had a response, as determined by the prescriber.
Note: The 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. The patient has tried at least one corticosteroid; AND
Note: An example is prednisone.

ii. The patient has tried at least one immunosuppressive agent; AND
Note: Examples include methotrexate (MTX), azathioprine, cyclosporine, Leukeran or Thalomid® (thalidomide capsules) or chloroquine.

iii. The agent is prescribed by or in consultation with a pulmonologist, ophthalmologist, or dermatologist.

B) Patients Currently Receiving an Infliximab Product. Approve for 1 year if the patient has 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. The 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 IV corticosteroids (such as prednisone, prednisolone, methylprednisolone); methotrexate (MTX); cyclosporine; or other immunosupressants.

ii. The agent is prescribed by or in consultation with an ophthalmologist.

B) Patients Currently Receiving an Infliximab Product. Approve for 1 year if the patient has had a responseas 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. The patient has tried one corticosteroid; AND
Note: An example is prednisone.

ii. The patient has tried one conventional synthetic disease-modifying antirheumatic drug (DMARD) given for at least 2 months or was intolerant to a conventional synthetic DMARD; AND
Note: An example is methotrexate.

iii. The agent is prescribed by or in consultation with a rheumatologist.

B) Patients Currently Receiving an Infliximab Product. Approve for 1 year if the patient has had a response, as determined by the prescriber.
Note: The patient may not have a full response by Month 2 or 3, but there should be some response.

17. Spondyloarthritis (SpA), Other Subtypes (Note: Examples of other subtypes include undifferentiated arthritis, non-radiographic axial SpA, Reactive Arthritis [Reiter's disease]. 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):

E) 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 disease-modifying antirheumatic drug (DMARD) has been tried; OR
Note: Examples include methotrexate [MTX], leflunomide, sulfasalazine.

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. The agent is prescribed by or in consultation with a rheumatologist.

F) Patients Currently Receiving an Infliximab Product. 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, 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. The 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 (MTX), 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 (e.g., Enbrel) or an adalimumab product (e.g., Humira) for uveitis. These patients who have already tried a biologic for uveitis are not required to try another agent).

ii. The agent is prescribed by or in consultation with an ophthalmologist.

B) Patients Currently Receiving an Infliximab Product. Approve for 1 year if the patient has had a responseas 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 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 with combinations and lack controlled trial data in support of additive efficacy.[34-35] 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, MMF, 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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OVERVIEW OF DISEASE STATE FOR PRIOR AUTHORIZATION DOCUMENT

Subject: Inflammatory Conditions – Juvenile Idiopathic Arthritis

Date Revised: 05/16/2017

Juvenile idiopathic arthritis (JIA) [previously referred to as juvenile rheumatoid arthritis {JRA}] is a broad term referring to a group of disorders characterized by chronic arthritis diagnosed in children less than 16 years of age with arthritis for at least 6 weeks and with other causes of arthritis excluded.[1-4,6] The International League of Associations for Rheumatology (ILAR) classification system of JIA with frequency is as follows: oligoarticular (persistent or extended) [50% to 60%]; polyarticular (rheumatoid factor negative or positive) [30% to 35%]; systemic (10% to 20%); psoriatic (2% to 15%); enthesitis-related (ankylosing spondylitis, arthritis associated with inflammatory bowel disease) [1% to 7%]; and other.[2] The subtypes are recognized based on the clinical features during the first 6 months of disease. Radiologic joint damage occurs in most patients with systemic onset and polyarticular arthritis within 2 years and in oligoarticular arthritis within 5 years.[1] Many patients continue to have active disease as adults.

Since JIA is not one disease, the treatment varies between the subtypes.[1-3] Disease modifying antirheumatic drugs (DMARDs) that have been effective in JIA include conventional synthetic DMARDs (i.e., sulfasalazine, methotrexate [MTX], leflunomide), tumor necrosis factor inhibitors (TNFis) [i.e., etanercept subcutaneous [SC] injection [e.g., Enbrel®, Erelzi™], adalimumab SC injection [e.g., Humira®, Amjevita™], infliximab intravenous [IV] infusion [e.g., Remicade®, Inflectra™, Renflexis®]), an inhibitor of T cell costimulation (i.e., Orencia® [abatacept IV infusion, abatacept SC injection], interleukin (IL)-1 blockers (i.e., Kineret® [anakinra SC injection], Ilaris® [canakinumab SC injection]), and an IL-6 blocker (i.e., Actemra™ [tocilizumab IV infusion]).[5] Some DMARDs may be effective in certain situations. For example, sulfasalazine may be effective in late-onset oligoarticular arthritis and in juvenile spondyloarthropathy. MTX may be effective in patients with a history of arthritis in five or more joints or in patients with arthritis in four or fewer joints. Leflunomide has also been effective in polyarticular JIA (PJIA) but experience is limited. Systemic JIA (SJIA) has systemic symptoms such as spiking fever, skin rash, hepatosplenomegaly or serositis and patients may or may not have active arthritis.[6-7] It is also associated with macrophage activation syndrome. When SJIA presents without active arthritis, it usually responds poorly to MTX.[5]

The 2011 American College of Rheumatology (ACR) recommendations for the treatment of JIA propose initial DMARD treatment with MTX in most patients; however, sulfasalazine is recommended for patients with enthesitis-related arthritis and may also be used in certain patients with sacroiliac arthritis.[5] Leflunomide may be an appropriate initial DMARD in certain patients with high disease activity and/or a poor prognosis. Kineret may be used in systemic arthritis. TNFis may be used for SJIA *with* active arthritis but have relatively poor effectiveness for SJIA with active systemic features *without* active arthritis. Patients with aggressive disease (e.g., sacroiliac arthritis) may be started early on a biologic agent. Orencia or a TNFi may be tried if initial treatment with a TNFi is unsuccessful. Rituxan® (rituximab for IV infusion) is also mentioned as an alternative for patients who have received sequential treatment with a TNFi and

Orencia. NSAIDs, systemic glucocorticoids, and Kineret are treatment options for patients with systemic arthritis with active systemic features *without* active arthritis. Updated guidelines from ACR were published for SJIA (2013).[7] The guidelines make recommendations for patients with active systemic features and varying degrees of synovitis based on the physician global assessment (MD global, on a 10-point visual analog scale [VAS] where 0 = no disease activity and 10 = the most severe) and active joint count (AJC = 0 joints, 1-4 joints, or > 4 joints). Based on the recommendations, Kineret is appropriate *initial therapy* in SJIA if the MD global is ≥ 5 (with any AJC) OR if MD global < 5 and AJC > 4 OR if MD global < 5 and AJC 1-4. Kineret is also considered an appropriate second- and third- line agent for all patients with SJIA (in patients with and without active systemic features). In patients with active systemic features and varying degrees of synovitis, Actemra and Ilaris are recommended for continued therapy in certain patients with disease activity following 1 month of Kineret, 2 weeks of therapy with glucocorticoids, or 1 month of NSAIDs, with exact treatment recommendations depending on physician global assessment and AJC. In patients without active systemic features and varying degrees of synovitis exact treatment recommendations also depend on physician global assessment and AJC. However, Orencia, Actemra, and a TNFi are options for certain patients with continued disease activity following 3 months of treatment with MTX or leflunomide. Orencia, TNFi, or Actemra are also options in certain patients with disease activity following 1 month of Kineret. There are also consensus treatment plans for new-onset SJIA developed by the Childhood Arthritis and Rheumatology Research Alliance (CARRA) specific for Actemra and Kineret.[8]

In clinical trials of JIA, response is often assessed using the ACR Pediatric (Pedi) 30 definition of improvement which is a ≥ 30% improvement in ≥ three of the six JIA core set variables with no more than one remaining variable worsening by > 30%.[4] The core set variables are: (1) physician global assessment of overall disease activity; (2) parent/patient global assessment of overall well-being (each scored on a 10 cm visual analog scale [VAS]); (3) functional ability; (4) number of joints with active arthritis; (5) number of joints with limited range of motion; (6) erythrocyte sedimentation rate (ESR); and (7) an absence of a spiking fever in the week prior to the evaluation (SJIA only).

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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.

1. 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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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® (anakinra for subcutaneous injection – Biovitrim)

DATE REVIEWED: 04/01/2020

OVERVIEW

Kineret is an interleukin-1 (IL-1) receptor antagonist indicated to reduce the signs and symptoms and slow the progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis (RA) who have failed one or more disease-modifying antirheumatic drugs (DMARDs).[1] Kineret is also indicated in Cryopyrin-Associated Periodic Syndromes (CAPS) for treatment of Neonatal-Onset Multisystem Inflammatory Disease (NOMID). In RA, Kineret can be used alone or in combination with DMARDs other than tumor necrosis factor inhibitors (TNFis).

Disease Overview

IL-1 production is induced in response to inflammation and mediates various physiologic responses including inflammatory and immunological responses.[1] In patients with RA, there are elevated amounts of IL-1 produced in the synovium and synovial fluid. Kineret blocks the biologic activity of IL-1 alpha and beta by competitively inhibiting IL-1 binding to the IL-1 type I receptor, which is expressed on a variety of cells. CAPS is a rare inherited inflammatory disease associated with overproduction of IL-1. In CAPS, spontaneous mutations in the CIAS1/NLRP3 gene leads to secretion of IL-1 beta, which has an important role in the systemic inflammation and manifestations of disease.

CAPS encompasses three rare genetic syndromes. Familial Cold Autoinflammatory Syndrome, Muckle-Wells Syndrome, and NOMID or chronic infantile neurological cutaneous and articular syndrome are thought to be one condition along a spectrum of disease severity.[2,3] There are no reliable prevalence statistics for CAPS, but the estimated number of persons with CAPS in the US is 200 to 500. In many cases, patients have had 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.

Guidelines

Il-1 blockers are mentioned in multiple guidelines for treatment of inflammatory conditions.

- Rheumatoid Arthritis: Current recommendations for the treatment of RA 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 RA and that TNFis and other non-TNFi biologics (i.e., rituximab, Actemra (tocilizumab IV infusion, tocilizumab SC injection], and Orencia [abatacept IV infusion, abatacept SC injection]) are appropriate initial biologic therapy for most patients with RA.
- 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).

Other Uses With Supportive Evidence

SJIA is a subtype of JIA characterized by arthritis of unknown origin and extra-articular symptoms such as spiking fever, macular rash, serositis, hepatosplenomegaly, and generalized lymphadenopahty due to reticuloendothelial involvement.[7] Macrophage activation syndrome (MAS) is a severe and potentially lethal complication associated with SJIA. Symptoms include non-remitting fever, hepatosplenomegaly, lymphadenopathy, encephalopathy, and coagulopathy and may also include multi-organ failure. Laboratory abnormalities may include pancytopenia, hyperferritinemia, hypertriglyceridemia, and elevated serum transaminases. There is insufficient evidence for the use of TNFis in MAS associated with SJIA. Case-series have shown rapid remission of MAS as well as treatment of the underlying condition with the use of Kineret. 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 (MTX).[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. **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 BOTH of the following criteria (i and ii):
     - **i.** The 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 (MTX), leflunomide, hydroxychloroquine, and sulfasalazine do not count.
     - **ii.** Kineret is prescribed by or in consultation with a rheumatologist.
   - **B)** Patients 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.

2. **Cryopyrin-Associated Periodic Syndromes (CAPS).** 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.** Kineret 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.** Kineret is prescribed by or in consultation with a rheumatologist, geneticist, or a dermatologist.
   - **B)** Patients Currently Receiving Kineret. 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 Kineret.

Other Uses with Supportive Evidence

3. **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)** The patient has tried one other systemic agent for this condition; OR

         Note: Examples of one other systemic agent 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 (e.g, Actemra IV), a tumor necrosis factor (TNF) inhibitor (e.g., an etanercept product, an adalimumab product, or an infliximab product), or Ilaris (canakinumab for SC injection) also counts towards a trial of one other systemic agent for SJIA.
       - **b)** The 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)** The patient has active systemic features with concerns of progression to macrophage activation syndrome (MAS), as determined by the prescriber; AND
     - **ii.** Kineret is prescribed by or in consultation with a rheumatologist.
   - **B)** Patients 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.

4. **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)** The patient meets ALL of the following criteria (1 and 2):
         - **(1)** The patient has tried one corticosteroid; AND
         - **(2)** The patient has had an inadequate response to 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.
           Note: A previous trial of a biologic (e.g., Actemra IV, Arcalyst, Ilaris) also counts towards a trial of one other systemic agent for Still's disease; OR
       - **b)** The patient has at least moderate to severe active systemic features of this condition, according to the prescriber.
         Note: Examples of moderate to severe active systemic features include fever, rash, lymphadenopathy, hepatomegaly, splenomegaly, and serositis; OR
       - **c)** The patient has active systemic features with concerns of progression to macrophage activation syndrome, as determined by the prescriber; AND
     - **ii.** Kineret is prescribed by or in consultation with a rheumatologist; OR
   - **B)** Patients 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

Kineret 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. **Ankylosing Spondylitis (AS).** Kineret has been beneficial in a few patients with AS, but results are not consistent.[15,16] In a small open-label study, patients with active AS 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 AS (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.

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. **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, MTX, 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 (OA), Symptomatic.** In a Phase II study in patients with painful OA 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 since there was no control group. Intraarticular injections are often associated with a significant placebo effect. Patients with OA 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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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 – 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

17. 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:

192. 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.

193. 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.

194. COVID-19 (Coronavirus Disease 2019). Forward all requests to the Medical Director.
Note: This includes requests for cytokine release syndrome associated with COVID-19.

195. 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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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:

196. 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.

197. 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.

198. 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.

199. 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.

200. 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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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

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 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.

3. 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.

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 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:

201. 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.

202. 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).

203. 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.

204. **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.

205. 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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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

18. 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.

19. 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.)

206. 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.

207. 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.

208. 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.

209. 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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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.

OVERVIEW OF DISEASE STATE FOR PRIOR AUTHORIZATION DOCUMENT

Subject: Inflammatory Conditions – Plaque Psoriasis

Date Reviewed: 05/16/2017

Psoriasis is a multisystem disease that affects the skin and joints.[1-2] It is a chronic inflammatory skin disease with scaly, erythematous patches, papules, and plaques and is often pruritic. It affects > 3% of persons in the US (>6million people).[3] The disease primarily affects adults and occurs equally in men and women.[1-2]

In plaque psoriasis, the most common form of psoriasis (80% to 90% of patients), there are patches of thick, inflamed skin covered with a silvery scale that can cause significant pain and discomfort. These plaques usually occur on the elbows, knees, legs, scalp, lower back, trunk and buttocks. Psoriasis may also affect the fingernails, toenails, soft tissues of the genitals, and inside the mouth. About 80% of patients have mild to moderate disease and 20% have moderate to severe psoriasis affecting more than 5% of body surface area (BSA) or areas such as the palms of the hands, soles the feet, face or genitals.[1] About 1 million of the people with psoriasis also have psoriatic arthritis (PsA). Triggers that may cause flare-ups of psoriasis include infections, stress, medications (e.g., lithium, beta adrenergic blockers), and changes that dry the skin. Other forms of psoriasis besides plaque type include guttate, pustular, inverse, and erythrodermic. Psoriasis may be associated with considerable physical and/or psychological disabilities. Treatment of psoriasis depends on the severity of the disease; the extent of disease (BSA involved); type of psoriasis; location of the lesions; symptoms; the patient's response to previous therapy; accessibility to a dermatologist, hospital, and ultraviolet (UV) light facilities; and co-morbid disease states. Since psoriasis is a chronic disease, long-term safety of medications must be considered.

For plaque psoriasis, if the disease is limited, topical therapies with corticosteroids ± vitamin D analogs (e.g., calcipotriene calcitriol), tazarotene (Tazorac®, generics), anthralin, coal tar preparations, keratolytics (salicylic acid, lactic acid, urea), topical moisturizers and combinations or sequential use of these topical therapies are indicated.[2,5] However, for patients with chronic plaque psoriasis that does not respond to topical therapies or patients with more extensive disease, systemic therapy may be used. The traditional systemic agents for plaque psoriasis are methotrexate (MTX), acitretin tablets (Soriatane®, generics), and cyclosporine.[5] These medications may have significant adverse effects (e.g., hepatotoxicity, nephrotoxicity, teratogenicity). Other systemic agents have been investigated in psoriasis (e.g., azathioprine, tacrolimus, and mycophenolate mofetil). Phototherapy (e.g., ultraviolet B [UVB]) and photochemotherapy (psoralen and ultraviolet A **[**UVA] light [PUVA]) may also be used.[6-7] Acitretin is a first-line systemic agent for patients with chronic palmoplantar or pustular psoriasis, but it has a limited role in patients with plaque psoriasis.[7] Cyclosporine is a fast-acting agent commonly used for certain types of pustular or erythrodermic psoriasis. Cyclosporine is also used intermittently (up to 12 weeks) to control psoriasis flares. MTX may be used for plaque psoriasis; compared to cyclosporine, MTX has a moderate effect but can be used long-term. The biologics have established efficacy in plaque psoriasis. Narrow band (NB) UVB can be used in the physician's office or at home and is slightly less effective than PUVA.[1,6] The injectable biologic agents, etanercept subcutaneous [SC] injection (e.g., Enbrel®, Erelzi™), adalimumab SC injection (e.g., Humira®, Amjevita™), infliximab intravenous (IV) infusion (e.g., Remicade®, Inflectra™, Renflexis®), Stelara® (ustekinumab SC injection), Cosentyx® (secukinumab SC injection), Siliq™ (brodalumab SC injection), and Taltz® (ixekizumab SC injection) are options for patients who are candidates for phototherapy or systemic therapy, especially those who are intolerant of or unresponsive to traditional systemic agents.[7] Another agent available is Otezla® (apremilast tablets), an oral phosphodiesterase 4 (PDE4) inhibitor that is indicated for treatment patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.[12]

Long-term safety is an important consideration.[7] The long-term risks of PUVA, MTX, and cyclosporine increase with cumulative dose. Safety concerns with the biologics include serious infections such as sepsis and tuberculosis, autoimmune conditions such as lupus and demyelinating disorders, and lymphoma. Patients with PsA, regardless of skin involvement, may require systemic therapy with MTX or Stelara, Cosentyx, or a tumor necrosis factor inhibitor (TNFi) such as etanercept, adalimumab, or infliximab that are effective for both plaque psoriasis and PsA.[2,14-15] Of note, Simponi® (golimumab for SC injection) and Cimzia® (certolizumab pegol SC injection) are TNFis indicated for PsA, but not for plaque psoriasis.[8,16] Note that Otezla is also indicated in PsA, and it does <u>not</u> have warnings regarding serious infection and malignancy, which are listed for the biologics approved for PsA, nor does Otezla have warnings for organ toxicity and laboratory monitoring that are noted with MTX and leflunomide.[12] Warnings/Precautions for

Otezla include depression, weight decrease, and drug interactions with strong cytochrome P450 inducers, and the most commonly observed adverse events (AEs) [incidence ≥ 5%] were diarrhea, nausea, and headache.

Almost all well-controlled clinical trials of psoriasis treatment include patients with chronic plaque psoriasis and exclude less common types of psoriasis and those involving the palms and soles, scalp, and intertriginous areas.[1]

One of the methods used to evaluate psoriasis in clinical trials is the psoriasis area-and-severity index (PASI) score.[1,9-10] The PASI ranges from 0 (no psoriasis) to 72 (the most severe disease possible) and combines the scores for the degree of erythema, induration, desquamation, and the percentage of BSA impacted. A primary endpoint in clinical trials is the PASI 75 which is ≥ 75% reduction from the baseline PASI score. Patients usually attain meaningful disease and quality of life improvements with at least a 50% decrease in PASI score.[10] Psoriasis severity (plaque, scaling, erythema) is also evaluated via global assessments by the physician.[11] The static Physician Global Assessment (sPGA) is reported on a six- or seven-point scale (e.g., ranging from 5 = severe to 0 = none indicating the physician's overall assessment of psoriasis severity). Other dynamic PGA scales define the endpoint using scales such as "clear" or "minimal" or "almost clear". The Dermatology Life Quality Index (DLQI) has been used as a guide in patient management (e.g., for assessment of disease severity).[8]

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OVERVIEW OF DISEASE STATE FOR PRIOR AUTHORIZATION DOCUMENT

Subject: Inflammatory Conditions – Psoriatic Arthritis Overview for PA Policy

Date Revised: 03/24/2017

Psoriatic arthritis (PsA) is considered a spondyloarthropathy and is distinct from rheumatoid arthritis (RA) and other inflammatory arthritides.[1] PsA may be defined as an inflammatory arthritis associated with psoriasis.[2] PsA develops in approximately one-third of patients with psoriasis; however, up to 20% of patients with PsA develop symptoms of arthritis prior to skin manifestations of disease.[1] Patients with PsA may have joint inflammation and synovitis, enthesitis, dactylitis, spinal involvement, and skin and nail psoriasis. Manifestations of PsA are very heterogeneous and multiple tissues may be involved with varying degrees of severity.[3] Joint damage in PsA is a result of bone destruction, bone formation, and cartilage loss.[4] Data from rheumatology referral centers indicate erosive and deforming arthritis occurs in 40% to 60% of patients with PsA and may be progressive as early as within one year of diagnosis.[2] Arthritis mutilans is a rare form of PsA which occurs when osteolysis and destructive changes in the joint lead to functional loss of the joint and irreversible deformity.[5] In the general population, PsA may have a milder course.[2]

Assessments used for clinical evaluation of PsA include the American College of Rheumatology (ACR) scoring system which has been used as the primary endpoint in clinical trials.[2-3] The distal interphalangeal (DIP) joints of the hand and both the proximal interphalangeal and DIP joints of the feet are counted and assessed in PsA. The Disease Activity Score (DAS) is also used in PsA trials and accommodates the commonly involved DIP and carpal-metacarpal joints. The PsA Response Criteria (PsARC) were specifically developed for PsA; these criteria focus on peripheral manifestations of PsA and have a limited capacity to capture features distinctive to PsA such as dactylitis and enthesitis. For axial disease, disease activity may be measured with the Bath Ankylosing Spondylitis Disability Activity Index (BASDAI).[3] The PsA Joint Activity Index (PsAJAI) was developed to assess joint disease in PsA.[6] The Composite Psoriatic Disease Activity Index (CPDAI) was also developed to consider joint, skin, dactylitis, enthesitis and back involvement in PsA. The CPDAI was developed and included the following domains: peripheral arthritis, skin disease, enthesitis, dactylitis, and spinal disease. On this index, a total score from 0 to 15 is possible, with a score of 0 corresponding with no disease and a score of 3 corresponding with severe disease for each domain.[7] In clinical practice, measure of response such as joint tenderness and swelling, global and pain response measures, functional indices and acute phase reactants have been used for monitoring and appear responsive.[8] Ultrasound and magnetic resonance imaging (MRI) have also been shown to be effective in detecting enthesitis and inflammation of the joints in patients with PsA.[9] Predictors of progressive PsA include polyarticular disease, elevated acute phase reactants, physical disability, erosive joint disease, and lack of response to initial therapies.

Guidelines

The European League Against Rheumatism (EULAR) has updated guidelines for PsA (2015).[10] In peripheral arthritis, a conventional synthetic disease-modifying drug (DMARD) [methotrexate {MTX} preferred) should be initiated early. Use of MTX in the Norwegian DMARD registry and TICOPA trial are cited to support this recommendation. If there is an inadequate response to at least one conventional synthetic DMARD, a biologic (usually a tumor necrosis factor [TNF] blocker) should be started. This recommendation is supported by the long-term experience and established safety/efficacy balance of TNF blockers vs. other biologics. In patients with an inadequate response to one conventional synthetic DMARD

and when TNF blockers are not appropriate, an interleukin (IL)-12/23 blocker (e.g., Stelara® [ustekinumab subcutaneous {SC} injection) or IL-17 blocker (e.g., Cosentyx® [secukinumab SC injection]) should be considered. It is noted that long-term data are needed to fully appreciate the benefit/risk profile of IL blockers. In patients with peripheral arthritis who have an inadequate response to at least one conventional synthetic DMARD, and when biologics are not appropriate, a targeted synthetic DMARD (e.g., Otezla® [apremilast tablets]) may be considered. It was acknowledged that Otezla has relatively low efficacy, plus there is a lack of radiographic data with Otezla. Lack of comparative studies and the safety profile were used to support this recommendation. In patients with enthesitis, dactylitis, or axial disease, the initial DMARD recommended are biologics; according to current practice a TNF blocker would be used. The guidelines note that comparison across trials is difficult because different outcomes were used. For enthesitis/dactylitis, the longest clinical experience is with TNF blockers. For axial disease, limited data with Stelara and a lack of data with Cosentyx influenced this recommendation. In patients who fail to respond to a biologic, switching to another biologic should be considered, including switching between TNF blockers.

Drug therapy for PsA has also been recommended by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) [2015] which includes both rheumatologists and dermatologists.[3] Treatment recommendations are made focusing on the following clinical domains of PsA: peripheral arthritis, axial disease, enthesitis, dactylitis, skin, and nail disease. General recommendations (standard therapeutic route) are made considering the following groupings: TNF blokers (e.g., Cimzia® [certolizumab pegol SC injection], Enbrel® [etanercept SC injection], Humira® [adalimumab SC injection], an infliximab product (e.g., Remicade®, Inflectra™], Simponi® [golimumab SC injection]), IL-12/23 (e.g., Stelara), IL-17 (e.g., Cosentyx), and phosphodiesterase 4 (PDE4) inhibitor (e.g., Otezla). In peripheral arthritis, TNF blockers or Otezla are recommended before Stelara or Cosentyx. However, the recommendation for TNF blockers is a stronger recommendation than Otezla. In axial disease, a TNF blocker, Stelara, or Cosentyx are recommended (TNF blockers have a stronger recommendation). Otezla is not recommended in axial disease. In patients with enthesitis, a TNF blocker, Stelara, Cosentyx or Otezla are recommended, but TNF blockers and Stelara have stronger recommendations than Cosentyx and Otezla. In patients with dactylitis, Otezla is conditionally recommended on equal footing with conventional synthetic DMARDs (MTX, leflunomide, sulfasalazine), followed by a trial of a TNF blocker or Stelara. In dactylitis, there is also an expedited route that leads to a TNF blocker or Stelara prior to a trial of conventional synthetic DMARD or Otezla. Cosentyx is conditionally recommended as a switch biologic (after a TNF blocker or Stelara). In those with skin disease, Otezla is recommended on equal footing with conventional synthetic DMARDs (MTX, cyclosporine, acetretin, fumaric acid esters). In skin disease, a TNF blocker, Stelara, Cosentyx, or Otezla is recommended following one of these therapies or as an expedited therapeutic route. For nail disease, a TNF blocker, Stelara, Cosentyx, and Otezla are potential first-line treatments. However, biologics have a stronger recommendation than Otezla.

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OVERVIEW OF DISEASE STATE FOR PRIOR AUTHORIZATION DOCUMENT

Subject: Inflammatory Conditions – Rheumatoid Arthritis Overview for PA Policy

Date Revised: 03/24/2017

In 2010, the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) collaborative initiative developed new classification criteria for rheumatoid arthritis (RA).[1] In this criteria, "definite RA" is based on the confirmed presence of synovitis in at least one joint, absence of an alternative diagnosis to better explain the synovitis, and achievement of a score ≥ 6 (out of 10) from individual scores of four domains (number and site of involved joints, serologic abnormality, elevated acute-phase response, and symptom duration). This system focuses on diagnosis of earlier-stage disease rather than late-stage RA.

Disease modifying antirheumatic drugs (DMARDs) are indicated for reducing signs and symptoms and inhibiting the progression of structural damage in patients with RA.[2] Patients with newly diagnosed RA should be started on DMARD therapy as soon as the diagnosis is made since these drugs may alter the disease course. The goal of therapy is to achieve and maintain remission or low disease activity.[3-4] Patients with a poor prognosis have one or more of the following features of RA: functional limitation (e.g., Health Assessment Questionnaire Disability Index [HAQ-DI]); extraarticular disease such as the presence of rheumatoid nodules, RA vasculitis, or Felty's syndrome; positive rheumatoid factor or anti-cyclic citrullinated peptide (CCP) antibodies; or bony erosions by radiograph.[2] Drug therapy should be adjusted every 3 months until the desired target is achieved.[4] When clinical decisions are made, structural changes and functional impairment must both be considered, as well as composite measures of disease activity.

Conventional Synthetic DMARDs vs. Biologics for RA

RA is a life-long disease. There is general speculation that earlier treatment of RA results in better outcomes, partially because joint damage is largely irreversible, making *prevention* of damage an important

goal.[2] According to the ACR, early intensive therapy may provide the best opportunity to preserve function and health-related quality of life and reduce work-related disability. However, one ideal treatment strategy for all patients with RA has not been established. Results from recent trials, including the RA: Comparison of Active Therapies (RACAT) and the Treatment of EArly Rheumatoid Arthritis (TEAR) studies have demonstrated similar efficacy with triple conventional synthetic (cs)DMARD therapy and Enbrel® (etanercept for subcutaneous [SC] injection) + methotrexate (MTX) in certain patient populations with RA.[5-6] Refer to Tables 1 and 2 for listings of DMARDs for RA.

Table 1. Conventional Synthetic DMARDs in RA.

Traditional Synthetic DMARDs	
Trade Name	**Generic Name (route)**
Rheumatrex®, Trexall®, Otrexup®, Rasuvo®	methotrexate (MTX) [oral, injection], generics
Arava®	leflunomide (oral), generics
Azulfidine En-tabs®, Azulfidine®	sulfasalazine (oral), generics
generics, Plaquenil®	hydroxychloroquine (oral), generics
Minocin®	minocycline (oral), generics
Imuran®	azathioprine (oral), generics
Neoral®, Sandimmune®	cyclosporine (oral), generics
Cuprimine®, Depen®	d-penicillamine (oral)

Table 1 (continued). Conventional Synthetic DMARDs in RA.

Traditional Synthetic DMARDs	
Trade Name	**Generic Name (route)**
gold compounds	
Myochrysine®	gold sodium thiomalate (injection), generics
Ridaura®	auranofin (oral)

DMARDs – Disease-modifying antirheumatic drugs; RA – Rheumatoid arthritis.

Table 2. Biologics and Targeted Synthetic DMARD used in RA.

Brand (generic name)	Mechanism of Action	Grouping
Actemra® (tocilizumab for IV infusion)	Inhibition of IL-6	Non-TNF biologic
Actemra® (tocilizumab for SC injection)	Inhibition of IL-6	Non-TNF biologic
Xeljanz®, Xeljanz XR (tofacitinib tablets)	Inhibition of the JAK pathways	Targeted synthetic DMARD
Infliximab products (IV) [e.g., Remicade® Inflectra™]	Inhibition of TNF	Infused TNF
Simponi® Aria™ (golimumab for IV infusion)	Inhibition of TNF	Infused TNF
Cimzia® (certolizumab pegol for SC injection)	Inhibition of TNF	Self-administered TNF
Etanercept products (SC) [e.g., Enbrel®, Erelzi™]	Inhibition of TNF	Self-administered TNF
Adalimumab products (SC) [e.g., Humira®, Amjevita™]	Inhibition of TNF	Self-administered TNF
Simponi® (golimumab for SC injection)	Inhibition of TNF	Self-administered TNF
Orencia® (abatacept for IV infusion)	T-cell costimulation modulator	Non-TNF biologic
Orencia® (abatacept for SC injection)	T-cell costimulation modulator	Non-TNF biologic
Rituxan® (rituximab for IV infusion)	CD20-directed cytolytic antibody	Non-TNF biologic
Kineret® (anakinra for subcutaneous SC injection)	Inhibition of IL-1	Non-TNF biologic

IV – Intravenous; IL – Interleukin; TNF – Tumor necrosis factor; SC – Subcutaneous; PDE4 – Phosphodiesterase 4; JAK – Janus kinase.

Guidelines

Updated guidelines from ACR (2015) detail treatment strategies for patients with RA.[2] In DMARD-naïve patients, conventional synthetic DMARD monotherapy (preferably MTX) is recommended as the initial treatment in early and established disease. Following failure of DMARD monotherapy there are several recommended options, including tumor necrosis factor (TNF) blockers (e.g., Cimzia® [certolizumab pegol subcutaneous SC injection], Enbrel, Humira® [adalimumab SC injection], Remicade® [infliximab intravenous {IV} infusion], Simponi® [golimumab SC injection], Simponi Aria® [golimumab IV infusion]) or non-TNF biologics (Actemra® [tocilizumab IV infusion, tocilizumab SC injection], Orencia® [abatacept IV infusion, abatacept SC injection], Rituxan® [rituximab IV infusion]). Xeljanz® (tofacitinib tablets) is most commonly listed as a treatment option following at least two biologics. Note that Xeljanz is disadvantaged because of potential longer-term safety concerns. Also, there is less clinical experience as well as concerns of the actual benefit/risk profile with Xeljanz. These guidelines do not make recommendations for Kineret® (anakinra SC injection) due to infrequent use in RA and lack of new data. Of note, for groupings that include IV and SC products, no distinction is made based on route of administration. A change in therapy is generally recommended when the patient has moderately or highly active disease despite the previous therapy. Refer to Table 3.

Table 3. Recommendations from ACR 2015 Guidelines, Early and Established RA.[2]

Clinical Scenario	Major Treatment Recommendations
DMARD-naïve patients (low, moderate, or high disease activity)	Early and established RA: • Traditional DMARD, monotherapy*
Following failure with DMARD monotherapy	Early and established RA (**no order of preference**):ᴷ • Combination DMARDs^ • TNFi ± MTX • Non-TNF biologics ± MTX
Following failure of a single TNFi	• Non-TNF biologics ± MTX (**preferred first option**) • TNFi ± MTX
Following failure of multiple TNFis	• Non-TNF biologic ± MTX (**preferred first option**) • Xeljanz ± MTX
Following failure of a single non-TNF biologic	• Non-TNF biologic ± MTX
Following failure of one TNFi and one non-TNF biologic	• Non-TNF biologics ± MTX (**preferred first option**) • Xeljanz ± MTX
Following failure of multiple non-TNF biologics	• TNFi ± MTX (if TNFi-naïve) • Xeljanz ± MTX

DMARD – Includes methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF), and hydroxychloroquine (HCQ); ^ Includes double- or triple-therapy with MTX, SSZ, LEF, HCQ; TNFi – Tumor necrosis factor inhibitor; ᴷ Xeljanz ± MTX is also listed as an option for established RA only.

Updated RA guidelines from EULAR (2016) note that treatment decisions are based on disease activity and other patient factors such as progression of structural damage, comorbidities, and safety issues.[11] DMARDs should be started at diagnosis of RA, with MTX as part of the first treatment strategy. In patients with contraindications or an early intolerance to MTX, leflunomide or sulfasalazine should be considered. In every patient, the treatment goal should be sustained remission or low disease activity. Frequent monitoring (i.e., every 1 to 3 months) is recommended for active disease; therapy adjustments are recommended if no improvement within 3 months of starting a therapy or if the treatment target has not been reached after 6 months of on therapy. Glucocorticoids may be considered short-term when initiating or changing csDMARD therapy, but they should be tapered as soon as clinically feasible. Poor prognostic factors include: moderate to high disease activity after csDMARD therapy, high acute phase reactant levels, high swollen joint counts, presence of RF and/or ACPA (especially at high levels), presence of early erosions, and/or failure of ≥ two csDMARDs. In patients who do not have poor prognostic factors, if the treatment target is not reached with the first csDMARD strategy, other csDMARDs should be considered. In a patient with poor prognostic factors who fails to reach the treatment target following the first csDMARD, a biologic or targeted synthetic DMARD is recommended (current practice is a biologic). It is recommended that biologics and targeted synthetic DMARDs are given in combination with a csDMARD; however, IL-6 inhibitors and targeted synthetic DMARDs may have advantages in patients who cannot use csDMARDs. If one of these treatments is failed, another biologic or targeted synthetic DMARD with the same or different mechanism of action may be tried. Tapering may be considered in certain patients who are in persistent remission.

Treatment Strategy

Patients with RA should be treated with conventional synthetic DMARD(s) [monotherapy; combination therapy may be considered after monotherapy with a conventional synthetic DMARD] prior to receiving

a biologic for RA.[2] It is remarkable that the RA population is a heterogeneous population, often with many comorbidities that may need to be considered for drug therapy on a case-by-case basis (e.g., pregnancy, alcoholism, congestive heart failure, malignancy/history of malignancy, etc.).

Disease Assessment

The ACR criteria assess 68 joints for tenderness and 66 joints for swelling.[8] ACR definition of improvement in RA trials is defined as improvement in the joint counts and improvement in three of the following parameters: patient assessment, physician assessment, erythrocyte sedimentation rate (ESR), pain scale, and/or functional questionnaire. Improvement is denoted as either ACR 20, ACR 50, or ACR 70 which reflects either an improvement to the 20%, 50%, or 70% level in the parameters outlined. An ACR 20 response indicates a decrease of at least 20% in both the number of tender joints and the number of swollen joints, in addition to a 20% improvement in at least 3 of the following: the patient's global assessment of disease status, the patient's assessment of pain, the patient's assessment of physical function (measured with the Modified Stanford HAQ), the physician's global assessment of disease status, and the C-reactive protein (CRP) level. The ACR score, as a combined index, is not used in clinical practice to measure individual response to treatment or when following a patient over time. In clinical practice, individual response can be measured using many composite measures of disease activity which include joint assessments.[9] The DAS 28 is an assessment that uses tender joint count (28 joints), swollen joint count (28 joints), patient reported general health status on a visual analog scale (VAS), and uses either CRP or ESR. It is recommended that physicians measure and record RA disease activity as low, moderate, or high using a standardized scale or composite index (such as the DAS 28 [ESR or CRP]) at least yearly. In clinical studies, functional status/physical function is assessed using the HAQ. There are 20 questions in the HAQ from eight categories (dressing, rising, eating, walking, hygiene, reach, grip, and errands/chores) and the HAQ score is the mean of the highest score in each of the eight categories with a possible range of 0 to 3; the HAQ-DI is a weighted sum of the scale scores.[10]

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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

20. 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:

210. 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.

211. 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.

212. COVID-19 (Coronavirus Disease 2019). Forward all requests to the Medical Director.
Note: This includes requests for cytokine release syndrome associated with COVID-19.

213. 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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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 – Rituximab Intravenous Products for Rheumatoid Arthritis (RA)

- Rituxan® (rituximab for intravenous infusion – Genentech)
- Ruxience™ (rituximab-pvvr IV injection – Pfizer)
- Truxima® (rituximab-abbs injection for intravenous use – Celltrion/Teva)

DATE REVIEWED: 11/20/2019

OVERVIEW

Rituximab is a chimeric murine/human 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 non-Hodgkin's lymphomas (NHLs). B-cells are thought to play a role in the pathogenesis of rheumatoid arthritis (RA) and associated chronic synovitis.

Ruxience and Truxima are approved as biosimilar to Rituxan intravenous (IV), 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.

All approved rituximab intravenous products are indicated for treatment of the following conditions:

1. Non-Hodgkin lymphoma (NHL), for previously untreated follicular, CD20-positive disease, in combination with first-line chemotherapy, and in patients achieving a complete or partial response to Rituxan in combination with chemotherapy, as a single-agent maintenance therapy; AND
2. NHL, for relapsed or refractory, low-grade or follicular, CD20-positive, B-cell, disease; AND
3. NHL, 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; AND
4. NHL, for previously untreated diffuse large B-cell, CD20-positive disease, in combination with cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) or other anthracycline-based chemotherapy regimens; AND
5. 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.

In addition to the above indications, Rituxan IV and Ruxience are also indicated for the following condition:

1. Granulomatosis with polyangitis (GPA) [Wegener's granulomatosis {WG}] and microscopic polyangiitis (MPA) in adults, in combination with glucocorticoids.

Rituxan IV is also indicated for treatment of the following conditions:

1. Rheumatoid arthritis (RA), in adult patients with moderately to severely active disease, in combination with methotrexate (MTX) for patients who have had an inadequate response to one or more tumor necrosis factor inhibitors (TNFis); AND
2. Pemphigus vulgaris, for adults with moderate to severe.

Disease Overview

RA is a chronic, systemic, autoimmune, inflammatory disorder of unknown origin characterized by synovial inflammation.[8] RA causes joint swelling, stiffness, and tenderness which may lead to cartilage damage, bone erosions, and joint destruction, and is often associated with significant activity limitations and disability. Compared with patients who do not have RA, mortality is increased in patients with established RA with approximately 40% of deaths in the RA population attributed to cardiovascular causes such as ischemic heart disease or stroke.[9] RA is associated with a decreased quality of life and can contribute to reduced employment rates and increased costs of care.[8] B-cells are thought to play a role in the pathogenesis of RA and associated chronic synovitis.[1] In patients with RA, rituximab produces a rapid and sustained depletion of circulating and tissue-based B-cells. Most patients have near complete depletion within 2 weeks after the first dose; the majority have peripheral B-cell depletion for at least 6 months which is followed by gradual recovery.

Guidelines

Guidelines from the American College of Rheumatology (ACR) [2015] have TNFis (e.g., Cimzia® [certolizumab pegol for subcutaneous {SC} injection], etanercept products [e.g., Enbrel®], adalimumab products [e.g., Humira®], infliximab IV products [e.g., Remicade®, Renflexis, Inflectra], Simponi® [golimumab for SC injection], Simponi Aria® [golimumab for intravenous {IV} infusion]) and non-TNF biologics (i.e., Actemra® [tocilizumab for IV infusion, tocilizumab for SC injection], Orencia® [abatacept for IV infusion, abatacept for SC injection], and rituximab products [e.g., Rituxan, Truxima]), administered with or without MTX, equally positioned as a recommended therapy following a trial of a conventional synthetic disease-modifying antirheumatic drug (csDMARD) [e.g., MTX, leflunomide, hydroxychloroquine, sulfasalazine].[3]

Safety

Rituximab IV products have Boxed Warnings due to fatal infusion reactions, severe mucocutaneous reactions, hepatitis B virus (HBV) reactivation, and progressive multifocal leukoencephalopathy (PML). Deaths within 48 hours of rituximab infusions have been reported, primarily (80%) associated with the first infusion. Screen all patients for HBV infection and monitor during and after treatment with rituximab IV. Discontinue rituximab products in cases of HBV reactivation.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of rituximab IV for RA. The intent of this policy is to provide recommendations for use in RA only. 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 RA (i.e., a rheumatologist). All approvals for RA are provided for a duration of 1 month (where 1 month is equal to 30 days); all approvals for other indications are provided for 1 year in duration.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of rituximab IV products is recommended in those with RA who meet the following criteria:

Food and Drug Administration (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 1 month (which is adequate duration to administer one course of therapy) if the patient meets the following conditions (i, ii, and iii):
     - **i.** The patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months.
       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 for RA are not required to "step back" and try a conventional synthetic DMARD; AND
     - **ii.** The agent will not be used concurrently with another biologic or with a targeted synthetic DMARD.

     Note: Examples of biologics include Cimzia, adalimumab products, etanercept products, infliximab products, Simponi (Aria or SC), Actemra (IV or SC), Kevzara, Kineret, and Orencia (IV or SC). Examples of targeted synthetic DMARDs include Xeljanz/XR, Oluminat, and Rinvoq.
     - **iii.** Rituximab IV is prescribed by or in consultation with a rheumatologist.
   - **B)** Patient has already Received One or More Courses of Rituximab for Rheumatoid Arthritis (RA). 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.
       Note: For example, there will be a minimum of 16 weeks since the first dose of the previous rituximab course and the first dose of the next course of rituximab; AND
     - **ii.** If the patient has already received two or more courses of therapy, the patient has responded to therapy, as determined by the prescribing physician.
       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, and reduced dosage of corticosteroids.

2. **Indications Other than Rheumatoid Arthritis (RA).** Approve for 1 year.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Rituximab IV 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. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Coverage for RA 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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APPENDIX

Brand (generic name)	Mechanism of Action
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6
Kevzara® (sarilumab SC injection)	Inhibition of IL-6
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator
Rituximab IV Products (Rituxan®, biosimiars)	CD20-directed cytolytic antibody
Kineret® (anakinra SC injection)	Inhibition of IL-1
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23
Siliq™ (brodalumab SC injection)	Inhibition of IL-17
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist
Otezla® (apremilast tablets)	Inhibition of PDE4
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways

SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; 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

W) 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.)

214. 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.

215. 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]

216. 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]

217. 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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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® (golimumab injection for intravenous use – Janssen Biotech)

DATE REVIEWED: 10/16/2019

OVERVIEW

Simponi Aria is a recombinant human monoclonal antibody specific for human tumor necrosis factor alpha (TNFα).[1] It is indicated for the following conditions:

1. Rheumatoid arthritis (RA), in combination with methotrexate (MTX) for treatment of adult patients with moderately to severely active disease; AND
2. Ankylosing spondylitis (AS), in adults with active disease; AND
3. Psoriatic arthritis (PsA), in adults with active disease.

For patients with AS and PsA, Simponi Aria may be given alone or in combination with MTX or other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). For all approved conditions, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and/or other analgesics may be continued during treatment with Simponi Aria. Simponi Aria is a biologic that is administered by intravenous (IV) infusion by a healthcare professional. Efficacy has not been established for patients switching between the Simponi Aria and the subcutaneous (SC) formulation of golimumab (Simponi SC).

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 psoriasis, psoriatic arthritis, and rheumatoid arthritis (RA). Increased levels of TNF are found in the synovial fluid of patients with RA, JIA, AS, and PsA; TNF has an important role in both the pathologic inflammation and the joint destruction that are characteristic of this disease. In psoriasis, increased levels of TNF are found in the blood and skin lesions. Simponi Aria neutralize the biological activity of TNFα and inhibits binding of TNFα with its receptors.

Guidelines

TNFis feature prominently in guidelines for treatment of inflammatory conditions.

- Ankylosing Spondylitis: 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 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.[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]

Safety

Simponi Aria has Boxed Warnings concerning risks of serious infection and the risk of malignancy.[1] Prior to initiating therapy with Simponi Aria, 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 Aria and if a serious infection or sepsis develops, Simponi Aria should be discontinued. Lymphoma and other malignancies have been reported in patients who have taken TNFis such as Simponi Aria.

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 (AEs) 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
Coverage of Simponi Aria is recommended in those who meet one the following criteria:

Food and Drug Administration (FDA)-Approved Indications

1. **Ankylosing Spondylitis (AS).** Approve Simponi Aria 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 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 (SC or Aria).

X) **Psoriatic Arthritis (PsA).** Approve Simponi Aria 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)** 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 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 [CRP]). The patient may not have a full response, but there should have been a recent or past response to Simponi (SC or Aria).

Y) **Rheumatoid Arthritis (RA).** Approve Simponi Aria 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 (e.g., Cimzia [certolizumab pegol SC injection], an etanercept product, an adalimumab product, an infliximab product, Simponi SC, Actemra [IV or SC], Kevzara [sarilumab SC injection], Kineret [anakinra SC injection], Orencia [abatacept IV infusion, abatacept SC injection], and a rituximab product). 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 Simponi (Aria or SC). 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 SC).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Simponi Aria 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.~~ **Concurrent Use with a 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., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Simponi Aria.

8. Ulcerative Colitis (UC). Simponi SC is indicated for treatment of UC.[5] A single-dose induction study in patients with UC (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 UC 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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APPENDIX

Brand (generic name)	Mechanism of Action
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF
Enbrel® (etanercept SC injection)	Inhibition of TNF
Erelzi™ (etanercept-szzs SC injection)	Inhibition of TNF
Humira® (adalimumab SC injection)	Inhibition of TNF
Amjevita® (adalimumab-atto SC injection)	Inhibition of TNF

Cyltezo™ (adalimumab-adbm SC injection)	Inhibition of TNF
Simponi® (golimumab SC injection)	Inhibition of TNF
Simponi® Aria™ (golimumab IV infusion)	Inhibition of TNF
Remicade® (infliximab IV infusion)	Inhibition of TNF
Inflectra™ (infliximab-dyyb IV infusion)	Inhibition of TNF
Renflexis® (infliximab-abda IV infusion)	Inhibition of TNF
Actemra® (tocilizumab IV infusion)	Inhibition of IL-6
Actemra® (tocilizumab SC injection)	Inhibition of IL-6
Kevzara® (sarilumab SC injection)	Inhibition of IL-6
Orencia® (abatacept IV infusion)	T-cell costimulation modulator
Orencia® (abatacept SC injection)	T-cell costimulation modulator
Rituxan® (rituximab IV infusion)	CD20-directed cytolytic antibody
Truxima® (rituximab-abbs IV infusion)	CD20-directed cytolytic antibody
Ruxience™ (rituximab-pvvr IV infusion)	CD20-directed cytolytic antibody
Kineret® (anakinra SC injection)	Inhibition of IL-1
Stelara® (ustekinumab SC injection)	Inhibition of IL-12/23
Stelara® (ustekinumab IV infusion)	Inhibition of IL-12/23
Siliq™ (brodalumab SC injection)	Inhibition of IL-17
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A
Ilumya™ (tildrakizumab-asmn for SC injection)	Inhibition of IL-23
Skyrizi™ (risankizumab SC injection)	Inhibition of IL-23
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways
Rinvoq™ (upadacitinib extended-release tablets)	Inhibition of the JAK pathways
Otezla® (apremilast tablets)	Inhibition of PDE4
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways

SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin;PDE4 – Phosphodiesterase 4; JAK – Janus kinase.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Selected revision	Update previous therapy required in the RA criteria. Criteria now require a trial of a conventional synthetic DMARD. There is an exception for patients who have already tried a biologic; these patients are not required to "step back" and try a conventional synthetic DMARD. Remove requirement that Simponi Aria be taken in combination with a conventional synthetic DMARD such as MTX. Remove other exceptions for patients who are not required to try a conventional synthetic DMARD prior to this biologic.	01/06/2016
Annual revision	No changes to criteria.	09/14/2016
Annual revision	No changes to criteria; however, Kevzara is added to list of examples of a previous therapy and Remicade is changed to "an infliximab product" with Remicade, Renflexis, and Inflectra listed as examples of specific infliximab products that may have been tried.	09/13/2017
Selected revision	Add AS and PsA with criteria for approval. Remove AS and PsA from the Conditions not Recommended for Coverage.	11/01/2017
Annual revision	For Patients Currently Receiving Simponi Aria or SC, 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

* 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; DMARDs – Disease-modifying antirheumatic drugs; RA – Rheumatoid arthritis; AS – Ankylosing spondylitis; PsA – Psoriatic arthritis.

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

Z) 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).

AA) 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).

BB) 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).

CC) 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

DD) 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.

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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)

REVIEW 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

EE) 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.)

218. 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.

219. 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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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® (ustekinumab intravenous infusion – Janssen Biotech)

REVIEW DATE: 09/11/2019; selected revision 10/23/2019

OVERVIEW

Stelara for intravenous (IV) infusion is a human immunoglobulin G (IgG) 1κ monoclonal antibody against the p40 subunit of the interleukin (IL)-12 and IL-23 cytokines.[1] It is indicated for the treatment of patients ≥ 18 years of age with the following indications:

1. Crohn's disease, in patients with moderate to severe active disease; AND

2. 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 IV infusion. Following induction therapy with the IV product, the recommended maintenance is Stelara for subcutaneous (SC) injection, given as a 90 mg SC injection administered 8 weeks after the initial IV dose, then once every 8 weeks (Q8W) thereafter.

Disease Overview

The P40 subunit of the IL-12 and IL-23 cytokines are involved in inflammatory and immune responses.[1] Stelara SC binds to the P40 subunit of used by both the IL-12 and IL-23 cytokines. By binding to this location, Stelara SC disrupts IL-12 and -23 mediated signaling and cytokine cascade. The IL-12 and -23 cytokines have been implicated as important contributors to the chronic inflammation that is observed in inflammatory bowel disease (Crohn's disease and ulcerative colitis).By blocking IL-12 and -23, Stelara may control the inflammatory response in patients with these conditions.

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 TNFi). Stelara is not addressed in the 2019 ACG guidelines for UC.[3] 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, Xeljanz, or TNFis (adalimumab, Simponi SC, infliximab).

Safety

Stelara has Warnings concerning risks of serious infection and the risk of malignancy.[1] Prior to initiating therapy with Stelara, patients should be evaluated for active tuberculosis (TB) infection. Patients should also be monitored for signs and symptoms of infection during treatment with Stelara, and if a serious infection develops, it should be stopped until the infection resolves.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Stelara IV. Because of the specialized skills required for evaluation and diagnosis of patients treated with Stelara as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Stelara IV 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 IV 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):
- **i.** The patient is 18 years of age or older; AND
- **ii.** Stelara IV will be used as induction therapy; AND
- **iii.** The patient meets one of the following conditions (i or ii):

a) The patient has tried or is currently taking corticosteroids, or corticosteroids are contraindicated in this patient; OR

b) The patient has tried one other agent for Crohn's disease.
Note: Examples of other agents for Crohn's disease include azathioprine, 6-mercaptopurine (6-MP), or methotrexate (MTX). A previous trial of a biologic (e.g., Cimzia® [certolizumab pegol SC injection], Entyvio [vedolizumab for IV infusion], an adalimumab product, or an infliximab product) also counts as a trial of one other agent for Crohn's disease; AND

iv. Stelara IV 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) The patient is 18 years of age or older; AND

B) Stelara IV will be used as induction therapy; AND

C) The patient has had a trial of one systemic agent for ulcerative colitis.
Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone or methylprednisolone. A trial of a biologic (e.g., an adalimumab product, an infliximab product, Simponi® [golimumab for SC injection], or Entyvio [vedolizumab injection]) also counts as a trial of one systemic agent for UC; AND

D) The agent is prescribed by or in consultation with a gastroenterologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Stelara 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.)

5. Ankylosing Spondylitis (AS). There are other biologic therapies indicated in AS (e.g., Cimzia, etanercept products [Enbrel], adalimumab products [Humira], infliximab products [Remicade, biosimilars], Simponi SC, Cosentyx [secukinumab SC injection], and Taltz [ixekizumab 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 SC 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 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 (ITT) 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 (MRI) 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 IV 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., MTX, 6-MP, azathioprine, and sulfasalazine) in combination with Stelara IV.

7. **Children or Adolescents < 18 Years of Age.** Stelara IV 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 SC injection is indicated for treatment of plaque psoriasis.[1] Appropriate dosing of Stelara IV in plaque psoriasis is unclear.

9. **Psoriatic Arthritis.** Stelara for SC injection is indicated for treatment of psoriatic arthritis.[1] Appropriate dosing of Stelara IV 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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APPENDIX

Brand (generic name)	Mechanism of Action
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6
Kevzara® (sarilumab SC injection)	Inhibition of IL-6
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator
Rituximab IV Products (Rituxan®, biosimiars)	CD20-directed cytolytic antibody
Kineret® (anakinra SC injection)	Inhibition of IL-1
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23
Siliq™ (brodalumab SC injection)	Inhibition of IL-17
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist
Otezla® (apremilast tablets)	Inhibition of PDE4
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways

SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; 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):

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

v. Patient is ≥ 18 years of age; AND

vi. 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.

vii. 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

viii. 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 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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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 Prior Authorization Policy
- Taltz® (ixekizumab for subcutaneous injection – Eli Lilly and Company)

REVIEW DATE: 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.
- **Non-radiographic axial spondyloarthritis**, in adults with active disease and objective signs of inflammation.

- **Plaque psoriasis**, in patients ≥ 6 years of age with moderate to severe disease who are candidates for systemic therapy or phototherapy.
- **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

FF) 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.

GG) 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.

HH) 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

Coverage of Taltz is not recommended in the following situations:

220. 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.

221. 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]

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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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

II) 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.

JJ) 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:

223. 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.

224. 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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36. Nast A, Gisondi P, Ormerod AD, et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris – Update 2015 – Short version – EDF in cooperation with EADV and IPC. *J Eur Acad Dermatol Venereol*. 2015;29(12):2277-2294.
37. 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.

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/tofacitinib extended-release tablets – Pfizer)

REVIEW DATE: 07/15/2020

OVERVIEW

Xeljanz/Xeljanz XR is an inhibitor of the Janus kinases (JAK) pathways approved for the following uses:[1]

- **Psoriatic arthritis**, for treatment of patients who have had an inadequate response or intolerance to methotrexate or other disease-modifying antirheumatic drugs (DMARDs). In psoriatic arthritis, Xeljanz/XR should be used in combination with a conventional synthetic DMARD.
- **Rheumatoid arthritis**, for treatment of adults with moderately to severely active disease who have had an inadequate response or intolerance to methotrexate, either as monotherapy or in combination with methotrexate or other nonbiologic DMARDs.
- **Ulcerative colitis**, for treatment of adults with moderately to severely active disease who have had an inadequate response or who are intolerant to tumor necrosis factor inhibitors (TNFis).

Safety and efficacy have not been established in patients < 18 years of age. For all indications, 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/XR if adequate therapeutic response is not achieved by Week 16.

- **Psoriatic Arthritis:** Guidelines from American College of Rheumatology (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.[2]
- **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).[3]
- **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).[4] Guidelines from the American Gastroenterological Association (2020) recommend Xeljanz only after failure of or intolerance to a TNFi.[5]

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 patients treated with Xeljanz 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/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

21. Psoriatic 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 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. These patients who have already tried a biologic are 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/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.** 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 Xeljanz/XR.

22. Rheumatoid Arthritis. Approve for the duration noted if the patient meets ONE of the following criteria (A or B):
- **C)** 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. 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.

D) 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.

23. Ulcerative Colitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

C) 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.

D) Patient is Currently Receiving 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/XR.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xeljanz/Xeljanz XR is not recommended in the following situations:

225. 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.[7-8] 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.

226. 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 MTX for RA; Xeljanz/Xeljanz XR has been evaluated in patients with RA taking background MTX, leflunomide, or combinations of DMARDs containing MTX and/or leflunomide.

227. COVID-19 (Coronavirus Disease 2019). Forward all requests to the Medical Director.
Note: This includes requests for cytokine release syndrome associated with COVID-19.

228. 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.[9] 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]

229. 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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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; 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

121. 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.

122. 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.)

230. 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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PRIOR AUTHORIZATION POLICY

POLICY: Iron Replacement – Feraheme® (ferumoxytol injection, for intravenous use – AMAG Pharmaceuticals)

DATE REVIEWED: 12/18/2019; selected revision 03/04/2020

OVERVIEW

Feraheme is an iron replacement product indicated for treatment of iron deficiency anemia in adult patients with chronic kidney disease (CKD), have an intolerance to oral iron, or have had unsatisfactory response to oral iron. Feraheme is administered by intravenous (IV) infusion and treatment may be repeated if iron deficiency remains persistent or recurring. The recommended dose of Feraheme is an initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later per treatment cycle.

Disease Overview

Iron deficiency anemia is a very broad diagnosis and can have many different etiologies; underlying causes should be corrected when appropriate. Anemia is generally characterized by a decrease in hemoglobin (Hb) or in the volume of red blood cells, which decrease the oxygen-carrying capacity in the blood.[2] Anemia is defined by the World Health Organization as Hb < 13.0 g/dL in men, < 12.0 g/dL in women, and < 11 g/dL during pregnancy.[2,3] Acute-onset anemia can present with tachycardia, lightheadedness, and shortness of breath.[2] Chronic anemia can manifest as weakness, fatigue, headache, dizziness, and pallor. Worldwide, iron deficiency is the most common nutritional deficiency. Anemia is prevalent in patients with CKD and the frequency and severity of anemia may increase with declining renal function. The severity and causes are variable and it can be a sign of other illnesses. Iron deficiency anemia is characterized by decreased levels of ferritin and serum iron, as well as decreased transferrin saturation (TSAT); decreases in Hb and hematocrit may follow.

Guidelines

The KDIGO guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[4] For adults with CKD and anemia not on iron or erythroid stimulating agent (ESA) therapy, a trial of 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 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.

Other Uses with Supportive Evidence

A 2017 focused update of the 2013 American College of Cardiology Foundation/American Heart Association guideline for the management of heart failure. It states that 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.[5] Benefits noted with IV iron therapies included improvement in functional capacity, improvements in the six-minute walk test and improved functional capacity.

The National Comprehensive Cancer Network guidelines on Hematopoietic Growth Factors (version 1.2020 – November 15, 2019) discuss the management of cancer- and chemotherapy-induced anemia.[6] 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%).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Feraheme. For patients with chronic kidney disease who are on dialysis, prior authorization is not required for prescription benefit coverage. 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 product meets the following criteria (A and B):
   - **A)** The 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)** The patient is ≥ 18 years of age; AND
   - **B)** The patient meets one of the following (i, ii, iii, or iv):
     - **i.** The patient meets both of the following (a and b):
       - **a)** The patient has tried oral iron supplementation; AND
       - **b)** According to the prescriber, oral iron supplementation was ineffective or intolerable; OR
     - **ii.** The patient has a condition which, per the prescriber, will interfere with oral iron absorption (e.g., inflammatory bowel disease, Crohn's disease); OR
     - **iii.** The 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 product meets the following criteria (A and B):
   - **A)** The 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

Feraheme 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.)

112. 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. Feraheme® [prescribing information]. Waltham, MA: AMAG Pharmaceuticals; February 2018.

178. Cook K, Ineck BA, Lyons WL. Anemias. In: Dipiro JT, Talbert RL, Yee GC, et al, (Eds). Pharmacotherapy – A Pathophysiologic Approach. 8th Ed, New York, NY: McGraw-Hill Companies, Inc. 2011:1717-1740.
179. Camaschella C. Iron deficiency. *Blood*. 2019;133(1):30-39.
180. 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.
181. 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.
182. 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 February 4, 2020.

PRIOR AUTHORIZATION POLICY

POLICY: Iron Replacement – Ferrlecit® (sodium ferric gluconate complex in sucrose injection, for intravenous use – sanofi-aventis)

DATE REVIEWED: 12/18/2019; selected revision 03/04/2020

OVERVIEW

Ferrlecit is an iron replacement product indicated for treatment of iron deficiency anemia in adults and pediatric patients ≥ 6 years of age with chronic kidney disease (CKD) receiving hemodialysis who are receiving supplemental epoetin therapy.[1] Ferrlecit is administered by intravenous (IV) infusion or slow injection and treatment may be repeated if iron deficiency remains persistent or recurring. The recommended dosage of Ferrlecit for the repletion treatment of iron deficiency in hemodialysis patients is 10 mL of Ferrlecit (125 mg of elemental iron). For repletion treatment most adult patients may require a cumulative dose of 1000 mg of elemental iron administered over 8 dialysis sessions. The recommended pediatric dosage in hemodialysis patients is 0.12 mL/kg Ferrlecit (1.5 mg/kg of elemental iron) administered by intravenous infusion per dialysis session. The maximum pediatric dosage should not exceed 125 mg per dose.

Disease Overview

Iron deficiency anemia is a very broad diagnosis and can have many different etiologies; underlying causes should be corrected when appropriate. Anemia is generally characterized by a decrease in hemoglobin (Hb) or in the volume of red blood cells, which decrease the oxygen-carrying capacity in the blood.[2] Anemia is defined by the World Health Organization as Hb < 13.0 g/dL in men, < 12.0 g/dL in women, and < 11 g/dL during pregnancy.[2,3] Acute-onset anemia can present with tachycardia, lightheadedness, and shortness of breath.[2] Chronic anemia can manifest as weakness, fatigue, headache, dizziness, and pallor. Worldwide, iron deficiency is the most common nutritional deficiency. Anemia is prevalent in patients with CKD and the frequency and severity of anemia may increase with declining renal function. The severity and causes are variable and it can be a sign of other illnesses. Iron deficiency anemia is characterized by decreased levels of ferritin and serum iron, as well as decreased transferrin saturation (TSAT); decreases in Hb and hematocrit may follow.

Guidelines

The KDIGO guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[4] For adults with CKD and anemia not on iron or erythroid stimulating agent (ESA) therapy, a trial of 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 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.

Other Uses with Supportive Evidence

A 2017 focused update of the 2013 American College of Cardiology Foundation/American Heart Association guideline for the management of heart failure. It states that 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 TSAT is < 20%), and with or without anemia, IV iron replacement may be reasonable to improve functional status and quality of life.[5] Benefits noted with IV iron therapies included improvement in functional capacity and improvements in the six-minute walk test.

The National Comprehensive Cancer Network guidelines on Hematopoietic Growth Factors (version 1.2020 – November 15, 2019) discuss the management of cancer- and chemotherapy-induced anemia.[6] 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%).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Ferrlecit. For patients with chronic kidney disease who are on dialysis, prior authorization is not required for prescription benefit coverage. 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.

6. **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are not on Dialysis**. Approve for 1 year if the product meets the following criteria (A and B):
   - **C)** The patient is ≥ 6 years of age; AND
   - **D)** Ferrlecit is prescribed by, or in consultation with, a nephrologist or hematologist.

Other Uses with Supportive Evidence

7. **Iron Deficiency Anemia, Other.** Approve for 1 year if the patient meets the following (A and B):
   - **C)** The patient is ≥ 6 years of age; AND
   - **D)** The patient meets one of the following (i, ii, iii, or iv):
     - **i.** The patient meets both of the following (a and b):
       - **a)** The patient has tried oral iron supplementation; AND
       - **b)** According to the prescriber, oral iron supplementation was ineffective or intolerable; OR
     - **ii.** The patient has a condition which, per the prescriber, will interfere with oral iron absorption (e.g., inflammatory bowel disease, Crohn's disease); OR
     - **iii.** The 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 product meets the following criteria (A and B):

C) The 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

Ferrlecit 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.)

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

REFERENCES

183. Ferrlecit® [prescribing information]. Bridgewater, NJ: sanofi-aventis; September 2019.
184. Cook K, Ineck BA, Lyons WL. Anemias. In: Dipiro JT, Talbert RL, Yee GC, et al, (Eds). Pharmacotherapy – A Pathophysiologic Approach. 8th Ed, New York, NY: McGraw-Hill Companies, Inc. 2011:1717-1740.
185. Camaschella C. Iron deficiency. *Blood*. 2019;133(1):30-39.
186. 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.
187. 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.
188. 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 February 4, 2020.

PRIOR AUTHORIZATION POLICY

POLICY: Iron Replacement – INFeD® (iron dextran injection, for intravenous or intramuscular use – Actavis Pharma)

DATE REVIEWED: 12/18/2019; selected revision 03/04/2020

OVERVIEW

INFeD is an iron replacement product indicated for treatment of iron deficiency anemia in whom oral administration is unsatisfactory or impossible. INFeD is administered by intravenous (IV) or intramuscular injection and treatment may be repeated if iron deficiency remains persistent or recurring. The INFeD prescribing information gives formulas and table guides for individualized dosages.

Disease Overview

Iron deficiency anemia is a very broad diagnosis and can have many different etiologies; underlying causes should be corrected when appropriate. Anemia is generally characterized by a decrease in hemoglobin (Hb) or in the volume of red blood cells, which decrease the oxygen-carrying capacity in the blood.[2] Anemia is defined by the World Health Organization as Hb < 13.0 g/dL in men, < 12.0 g/dL in women, and < 11 g/dL during pregnancy.[2,3] Acute-onset anemia can present with tachycardia, lightheadedness, and shortness of breath.[2] Chronic anemia can manifest as

weakness, fatigue, headache, dizziness, and pallor. Worldwide, iron deficiency is the most common nutritional deficiency. Anemia is prevalent in patients with chronic kidney disease (CKD) and the frequency and severity of anemia may increase with declining renal function. The severity and causes are variable and it can be a sign of other illnesses. Iron deficiency anemia is characterized by decreased levels of ferritin and serum iron, as well as decreased transferrin saturation (TSAT); decreases in Hb and hematocrit may follow.

Guidelines

The KDIGO guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[4] For adults with CKD and anemia not on iron or erythroid stimulating agent (ESA) therapy, a trial of 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 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.

Other Uses with Supportive Evidence

A 2017 focused update of the 2013 American College of Cardiology Foundation/American Heart Association guideline for the management of heart failure. It states that 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 TSAT is < 20%), and with or without anemia, IV iron replacement may be reasonable to improve functional status and quality of life.[5] Benefits noted with IV iron therapies included improvement in functional capacity and improvements in the six-minute walk test.

The National Comprehensive Cancer Network guidelines on Hematopoietic Growth Factors (version 1.2020 – November 15, 2019) discuss the management of cancer- and chemotherapy-induced anemia.[6] 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%).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of INFeD. For patients with chronic kidney disease who are on dialysis, prior authorization is not required for prescription benefit coverage. 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) The patient meets both of the following (i and ii):

i. The patient has tried oral iron supplementation; AND

ii. According to the prescriber, oral iron supplementation was ineffective or intolerable; OR

F) The patient has a condition which, per the prescriber, will interfere with oral iron absorption (e.g., inflammatory bowel disease, Crohn's disease); OR
G) The 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 product is prescribed by, or in consultation with, a nephrologist or hematologist.

12. Iron Deficiency Associated with Heart Failure. Approve for 1 year if the product is being prescribed by, or in consultation with, a cardiologist or hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

INFeD 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.)

114. 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. INFeD® [prescribing information]. Parsippany, NJ: Actavis Pharma; September 2019.
190. Cook K, Ineck BA, Lyons WL. Anemias. In: Dipiro JT, Talbert RL, Yee GC, et al, (Eds). Pharmacotherapy – A Pathophysiologic Approach. 8th Ed, New York, NY: McGraw-Hill Companies, Inc. 2011:1717-1740.
191. Camaschella C. Iron deficiency. *Blood*. 2019;133(1):30-39.
192. 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.
193. 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.
194. 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 February 4, 2020.

PRIOR AUTHORIZATION POLICY

POLICY: Iron Replacement – Injectafer® (ferric carboxymaltose injection, for intravenous use – American Regent)

DATE REVIEWED: 12/18/2019; selected revision 03/04/2020

OVERVIEW

Injectafer is an iron replacement product indicated for treatment of iron deficiency anemia in adult patients who have non-dialysis dependent chronic kidney disease (CKD), who have intolerance to oral iron, or have had unsatisfactory response to oral iron. Injectafer is administered by intravenous (IV) infusion or slow injection and treatment may be

repeated if iron deficiency remains persistent or recurring. The recommended dose is up to 750 mg per dose with a total cumulative dose not to exceed 1500 mg per treatment course.

Disease Overview

Iron deficiency anemia is a very broad diagnosis and can have many different etiologies; underlying causes should be corrected when appropriate. Anemia is generally characterized by a decrease in hemoglobin (Hb) or in the volume of red blood cells, which decrease the oxygen-carrying capacity in the blood.[2] Anemia is defined by the World Health Organization as Hb < 13.0 g/dL in men, < 12.0 g/dL in women, and < 11 g/dL during pregnancy.[2,3] Acute-onset anemia can present with tachycardia, lightheadedness, and shortness of breath.[2] Chronic anemia can manifest as weakness, fatigue, headache, dizziness, and pallor. Worldwide, iron deficiency is the most common nutritional deficiency. Anemia is prevalent in patients with chronic kidney disease (CKD) and the frequency and severity of anemia may increase with declining renal function. The severity and causes are variable and it can be a sign of other illnesses. Iron deficiency anemia is characterized by decreased levels of ferritin and serum iron, as well as decreased transferrin saturation (TSAT); decreases in Hb and hematocrit may follow.

Guidelines

The KDIGO guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[4] For adults with CKD and anemia not on iron or erythroid stimulating agent (ESA) therapy, a trial of 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 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.

Other Uses with Supportive Evidence

A 2017 focused update of the 2013 American College of Cardiology Foundation/American Heart Association guideline for the management of heart failure. It states that 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 TSAT is < 20%), and with or without anemia, IV iron replacement may be reasonable to improve functional status and quality of life.[5] Benefits noted with IV iron therapies included improvement in functional capacity and improvements in the six-minute walk test.

The National Comprehensive Cancer Network guidelines on Hematopoietic Growth Factors (version 1.2020 – November 15, 2019) discuss the management of cancer- and chemotherapy-induced anemia.[6] 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%).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Injectafer. For patients with chronic kidney disease who are on dialysis, prior authorization is not required for prescription benefit coverage. 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 on Dialysis**. Approve for 3 years.

14. **Iron Deficiency Anemia in Patients with Chronic Kidney Disease who are not on Dialysis**. Approve for 1 year if the product meets the following criteria (A and B):
    - **E)** The patient is ≥ 18 years of age; AND
    - **F)** Injectafer is prescribed by, or in consultation with, a nephrologist or hematologist.

15. **Iron Deficiency Anemia, Other.** Approve for 1 year if the patient meets the following (A and B):
    - **I)** The patient is ≥ 18 years of age; AND
    - **J)** The patient meets one of the following (i, ii, iii, or iv):
        - **i.** The patient meets both of the following (a and b):
            - **a)** The patient has tried oral iron supplementation; AND
            - **b)** According to the prescriber, oral iron supplementation was ineffective or intolerable; OR
        - **ii.** The patient has a condition which, per the prescriber, will interfere with oral iron absorption (e.g., inflammatory bowel disease, Crohn's disease); OR
        - **iii.** The 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

16. **Iron Deficiency Associated with Heart Failure.** Approve for 1 year if the product meets the following criteria (A and B):
    - **E)** The 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

Injectafer 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.)

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

REFERENCES

195. Injectafer® [prescribing information]. Shirley, NY: American Regent; April 2018.
196. Cook K, Ineck BA, Lyons WL. Anemias. In: Dipiro JT, Talbert RL, Yee GC, et al, (Eds). Pharmacotherapy – A Pathophysiologic Approach. 8th Ed, New York, NY: McGraw-Hill Companies, Inc. 2011:1717-1740.
197. Camaschella C. Iron deficiency. *Blood*. 2019;133(1):30-39.
198. 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.
199. 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.

200. 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 February 4, 2020.

PRIOR AUTHORIZATION POLICY

POLICY: Iron Replacement – Monoferric® (ferric derisomaltose injection for intravenous use – Pharmacosmos)

DATE REVIEWED: 03/04/2020

OVERVIEW

Monoferric is an iron replacement product indicated for treatment of iron deficiency anemia in patients ≥ 18 years of age with non-hemodialysis chronic kidney disease, have an intolerance to oral iron, or have had unsatisfactory response to oral iron. Monoferric is administered by intravenous (IV) infusion and treatment may be repeated if iron deficiency remains persistent or recurring. The recommended dose of Monoferric is 1000 mg in patients weighing ≥ 50 kg administered as a single dose per treatment cycle. For patients weighing < 50 kg, the recommended dose is 20 mg/kg administered as a single dose per treatment cycle.

Disease Overview

Iron deficiency anemia is a very broad diagnosis and can have many different etiologies; underlying causes should be corrected when appropriate. Anemia is generally characterized by a decrease in hemoglobin (Hb) or in the volume of red blood cells, which decrease the oxygen-carrying capacity in the blood.[2] Anemia is defined by the World Health Organization as Hb < 13.0 g/dL in men, < 12.0 g/dL in women, and < 11 g/dL during pregnancy.[2,3] Acute-onset anemia can present with tachycardia, lightheadedness, and shortness of breath.[2] Chronic anemia can manifest as weakness, fatigue, headache, dizziness, and pallor. Worldwide, iron deficiency is the most common nutritional deficiency. Anemia is prevalent in patients with chronic kidney disease (CKD) and the frequency and severity of anemia may increase with declining renal function. The severity and causes are variable and it can be a sign of other illnesses. Iron deficiency anemia is characterized by decreased levels of ferritin and serum iron, as well as decreased transferrin saturation (TSAT); decreases in Hb and hematocrit may follow.

Guidelines

The KDIGO guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[4] For adults with CKD and anemia not on iron or erythroid stimulating agent (ESA) therapy, a trial of 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 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.

Other Uses with Supportive Evidence

A 2017 focused update of the 2013 American College of Cardiology Foundation/American Heart Association guideline for the management of heart failure. It states that 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.[5] Benefits noted with IV iron therapies included improvement in functional capacity, improvements in the six-minute walk test and improved functional capacity.

The National Comprehensive Cancer Network guidelines on Hematopoietic Growth Factors (version 1.2020 – November 15, 2019) discuss the management of cancer- and chemotherapy-induced anemia.[6] 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%).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Monoferric. For patients with chronic kidney disease who are on dialysis, prior authorization is not required for prescription benefit coverage. 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 product meets the following criteria (A and B):
    - **G)** The 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)** The patient is ≥ 18 years of age; AND
    - **L)** The patient meets one of the following (i, ii, iii, or iv):
        - **i.** The patient meets both of the following (a and b):
            - **a)** The patient has tried oral iron supplementation; AND
            - **b)** According to the prescriber, oral iron supplementation was ineffective or intolerable; OR
        - **ii.** The patient has a condition which, per the prescriber, will interfere with oral iron absorption (e.g., inflammatory bowel disease, Crohn's disease); OR
        - **iii.** The 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 product meets the following criteria (A and B):
    - **G)** The 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

Monoferric 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.)

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

REFERENCES

201. Monoferric® injection [prescribing information]. Holbaek, Denmark: Pharmacosmos; January 2020.
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PRIOR AUTHORIZATION POLICY

POLICY: Iron Replacement – Venofer® (iron sucrose injection, for intravenous use – American Regent)

DATE REVIEWED: 12/18/2019; selected revision 03/04/2020

OVERVIEW

Venofer is an iron replacement product indicated for treatment of iron deficiency anemia in patients with chronic kidney disease (CKD).[1] Venofer is administered by intravenous (IV) infusion or slow injection and treatment may be repeated if iron deficiency remains persistent or recurring. Dosage and dosing frequency varies depending on patient age, if there is a need for dialysis, and, if needed, what type if dialysis (hemodialysis or peritoneal). The recommended maximum total course dose is 1000 mg per treatment cycle.

Disease Overview

Iron deficiency anemia is a very broad diagnosis and can have many different etiologies; underlying causes should be corrected when appropriate. Anemia is generally characterized by a decrease in hemoglobin (Hb) or in the volume of red blood cells, which decrease the oxygen-carrying capacity in the blood.[2] Anemia is defined by the World Health Organization as Hb < 13.0 g/dL in men, < 12.0 g/dL in women, and < 11 g/dL during pregnancy.[2,3] Acute-onset anemia can present with tachycardia, lightheadedness, and shortness of breath.[2] Chronic anemia can manifest as weakness, fatigue, headache, dizziness, and pallor. Worldwide, iron deficiency is the most common nutritional deficiency. Anemia is prevalent in patients with chronic kidney disease (CKD) and the frequency and severity of anemia may increase with declining renal function. The severity and causes are variable and it can be a sign of other

illnesses. Iron deficiency anemia is characterized by decreased levels of ferritin and serum iron, as well as decreased transferrin saturation (TSAT); decreases in Hb and hematocrit may follow.

Guidelines

The KDIGO guidelines for anemia in CKD (2012) make various recommendations regarding iron therapy.[4] For adults with CKD and anemia not on iron or erythroid stimulating agent (ESA) therapy, a trial of 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 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.

Other Uses with Supportive Evidence

A 2017 focused update of the 2013 American College of Cardiology Foundation/American Heart Association guideline for the management of heart failure. It states that 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.[5] Benefits noted with IV iron therapies included improvement in functional capacity, improvements in the six-minute walk test and improved functional capacity.

The National Comprehensive Cancer Network guidelines on Hematopoietic Growth Factors (version 1.2020 – November 15, 2019) discuss the management of cancer- and chemotherapy-induced anemia.[6] 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%).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Venofer. For patients with chronic kidney disease who are on dialysis, prior authorization is not required for prescription benefit coverage. 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 product 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) The patient meets both of the following (i and ii):
- **i.** The patient has tried oral iron supplementation; AND
- **ii.** According to the prescriber, oral iron supplementation was ineffective or intolerable; OR

N) The patient has a condition which, per the prescriber, will interfere with oral iron absorption (e.g., inflammatory bowel disease, Crohn's disease); OR

O) The 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 product is being prescribed by, or in consultation with, a cardiologist or hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Venofer 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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PRIOR AUTHORIZATION POLICY

POLICY: Keveyis® (dichlorphenamide tablets – Taro Pharmaceuticals)

DATE REVIEWED: 12/18/2019

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] The primary periodic paralyses are rare muscle disorders caused by genetic mutations in ion channels.[2] HypoPP is caused in 80% of cases by point mutations in the voltage-gated calcium channel gene on chromosome 1. Mutation in the *CACNA1S, SCN4A,* or *KCNJ18* genes alter the usual structure and function of calcium or

sodium channels.[3,4] 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.[3] HyperPP and HypoPP are inherited in an autosomal dominant manner, so one copy of the altered gene in each cell is sufficient to cause the disorder.[5] Other channelopathies include Andersen-Tawil syndrome, paramyotonia congenital, and potassium-aggravated myotonia.

The recommended initial dose of Keveyis is 50 mg once or twice daily.[1] The maximum recommended total daily dose is 200 mg. Primary HyperPP, primary HypoPP, and related variants are a heterogeneous group of conditions, for which the 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.

The normal serum potassium concentration ranges from 3.5 to 5.0 mEq/L, although there may be slight fluctuations in the normal range depending on the laboratory.[4] Generally, serum potassium concentration < 3.5 mEq/L is considered hypokalemia and serum potassium concentration > 5.0 mEq/L or 5.5 mEq/L is considered hyperkalemia.

Efficacy Data

The efficacy of Keveyis was established in two Phase III studies.[1,6,9] In both of these studies, when Keveyis was compared with placebo there was a statistically significant decrease in the attack frequency per week, severity-weighted attack rate, and the duration of attacks.

Other Drug Therapies

Oral potassium salts can be taken as maintenance/prophylactic therapy for patients with HypoPP; however, this does not completely prevent attacks.[4] Although data are limited to case reports and single-blind trials, acetazolamide, another carbonic anhydrase inhibitor, has been used historically for primary periodic paralysis. In one Keveyis published study, 40% of patients (n = 29/73) were receiving prophylactic treatment at baseline; 76% of these patients (n = 22/29) were taking acetazolamide and the rest were taking dichlorphenamide.[6] Acetazolamide treatment is beneficial in approximately 50% of patients with HypoPP and it has no effect in 30% of affected patients.[4] It can also exacerbate symptoms in 20% of patients. Keveyis has been reported to be 30 times more potent than acetazolamide *in vitro*.[9] 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.[7]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Keveyis. 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. 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 Keveyis is recommended in those who meet the following criteria:

FDA-Approved Indications

24. Hypokalemic Periodic Paralysis (HypoPP) and Related Variants.

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 (e.g., Diamox tablets, Diamox Sequels extended-release capsules, generics); AND
- **v.** According to the prescriber, acetazolamide therapy did not worsen the paralytic attack frequency or severity in the patient; AND
- **vi.** Keveyis 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) Patients Continuing Therapy. 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.

25. Hyperkalemic Periodic Paralysis (HyperPP) and Related Variants.

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 (e.g., Diamox tablets, Diamox Sequels extended-release capsules, generics); AND
- **iv.** According to the prescriber, acetazolamide therapy did not worsen the paralytic attack frequency or severity in the patient; AND
- **v.** Keveyis 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) Patients Continuing Therapy. 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

Keveyis 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.)

231. 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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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:

232. **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.

233. **Fibromyalgia.** There are no data available on the use of lidocaine patches in treating pain associated with fibromyalgia.

234. **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.

235. **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.

236. 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.

237. Rheumatoid Arthritis (RA). There are no data available on the use of lidocaine patches in treating pain associated with RA.

238. Sciatica. There are no data available on the use of lidocaine patches in treating pain associated with sciatica.

239. 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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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

E) 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):
  - **iv.** The patient is ≥ 18 years of age; AND
  - **v.** Egrifta is prescribed for the reduction of excess abdominal fat; AND
  - **vi.** 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
  - **vii.** 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

viii. 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).

D) 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.)

240. 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.

241. Human Immunodeficiency Virus (HIV)-Related Cachexia, Weight Loss, or Fat Distribution other than Lipodystrophy. Egrifta has not been studied in these conditions.

242. 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]

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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PRIOR AUTHORIZATION POLICY

POLICY: Lipodystrophy – Myalept® (metreleptin for subcutaneous injection – Aegerion)

REVIEW DATE: 09/25/2019

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 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 AEs 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 3 years in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

26. Generalized Lipodystrophy (Congenital or Acquired): Approve Myalept for 3 years in patients with generalized lipodystrophy if the medication is prescribed by, or in consultation with, an endocrinologist or a geneticist physician specialist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Myalept 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. 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.

245. 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.

246. 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]

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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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

27. Opioid Withdrawal Symptoms. Approve for 2 weeks (14 days) if the patient meets the following criteria (A and B):
- **72.** Lucemyra is being used to facilitate abrupt opioid discontinuation; AND
- **73.** 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:

248. 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.

249. 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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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

28. 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.

29. 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.)

250. Fibromyalgia. A double-blind, placebo-controlled, randomized withdrawal trial of Lyrica CR in adults with fibromyalgia failed to demonstrate efficacy.[1]

251. 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]

252. Restless Legs Syndrome. No data are available for Lyrica CR for the treatment of restless legs at this time.

253. 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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PRIOR AUTHORIZATION POLICY

POLICY: Makena® (hydroxyprogesterone caproate injection [subcutaneous and intramuscular] – AMAG, Pharmaceuticals, Inc.; generics [intramuscular only])

REVIEW DATE: 09/04/2019

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 (SPTB).[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. Limitations of Use: 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 (IM) at a dose of 250 mg (1 mL) once weekly or by the subcutaneous (SC) 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.

The efficacy and safety of Makena was established in one randomized, double-blind, multicenter, vehicle-controlled, pivotal study in women between the ages of 16 and 43 years.[1] Women were pregnant with a singleton pregnancy with a documented history of singleton SPTB, defined as delivery < 37 weeks gestation following spontaneous preterm labor or premature rupture of membranes (PROM). Major exclusion criteria included a pregnancy with multiple gestations. Patients were randomized between 16 weeks, 0 days gestation and 20 weeks, 6 days gestation. The primary endpoint was the proportion of women in each treatment arm who delivered at < 37 weeks gestation. The study took place in the US and was conducted with an investigational formulation of hydroxyprogesterone caproate identical to Makena.[2-3] Patients were assigned to treatment with Makena, 250 mg in 1 mL (n = 310), or vehicle (castor oil) [n = 153] in a 2:1 ratio.

There was a statistically significant reduction in the rate of delivery before 37 weeks gestation in patients treated with Makena compared with vehicle. The rates of delivery prior to Week 37 were similar for Black and non-Black women.[2-3] Among women of similar risk, the number-needed-to-treat (NNT) was 5 to 6 women (95% confidence interval [CI]: 3.6, 11.1) to prevent one preterm delivery prior to 37 weeks gestation. Patients treated with Makena also had statistically significant reductions in the rates of delivery prior to 35 weeks and 32 weeks gestation. A small increase in the rate of miscarriage and stillbirth occurred in the Makena group; however, this difference was not statistically significant compared with the patients treated with vehicle.

The approval of Makena for SC use was based on usability studies and one pharmacokinetic study that confirmed bioequivalence between the IM dosing regimen and the SC dosing regimen.[4]

Guidelines

The Society for Maternal-Fetal Medicine (SMFM) published guidelines (2012, reaffirmed 2014) regarding the use of progesterone in preterm birth prevention.[5] Intramuscular 17 alpha hydroxyprogesterone caproate (17P) is recommended for use in women with singleton pregnancy with prior history of spontaneous preterm birth (approved indication). A SMFM statement (2017) continued to recommend all women with a prior spontaneous preterm birth of a singleton pregnancy be offered 17P therapy in subsequent pregnancy with a singleton gestation.[6] Also included in this statement are discussions about women with a prior SPTB who start 17P and subsequently develop cervical shortening. It is unknown whether there is any benefit to change progestogen to vaginal progesterone (with or without cervical cerclage placement) in this circumstance. Based on data regarding the lack of benefit of vaginal progesterone in women with a history of a prior SPTB, the SMFM recommends the continuation of 17P in women with a history of a prior SPTB throughout pregnancy despite the development of cervical shortening (with or without cervical cerclage placement).[6]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Makena (and generics). All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Makena (SC or IM administration) 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 (SPTB) 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 (SC or IM) 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. **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.[7-8] 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.[9]

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.[10-12] 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% CI: 0.9, 1.5).[10] 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).[11] 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.[12] 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, IM 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.[13] 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.[14-16]

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. IM 17P is recommended for use in singleton pregnancies with prior spontaneous preterm birth (approved indication).[5,6]

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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PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Carbaglu (carglumic acid tablets for oral suspension – Orphan Europe, SARL/Recordati Rare Diseases)

DATE REVIEWED: 03/11/2020

OVERVIEW

Carbaglu is indicated in pediatric and adult patients, both as an adjunctive therapy for the treatment of acute hyperammonemia, and for maintenance therapy for chronic hyperammonemia, due to the deficiency of the hepatic enzyme N-acetylglutamate (NAGS). It is a synthetic structural analogue of N-acetylglutamate (NAG) thereby acting as a replacement for NAG in patients with NAGS deficiency. During acute hyperammonia, other therapies, including protein restriction, is recommended. During the maintenance therapy, concomitant use of other ammonia lowering therapies and protein restriction may be needed based on plasma ammonia levels.

Disease Overview

NAGS deficiency is one of the rarest urea cycle disorders.[2-3] NAGS is an enzyme that is located in the liver and intestine, and is essential for the function of the urea cycle. Although NAGS deficiency can be suspected based on patient/family history and high levels of ammonia in the blood, the diagnosis is confirmed by molecular genetic testing.[5] Of note, there are 12 gene mutations that have been identified resulting a NAGS deficiency. The neonatal-onset phenotype usually reflects complete absence of NAGS activity.[2-3] Symptoms result primarily from hyperammonemia. If newborns survive

the acute hyperammonemic episode, they typically go on to exhibit significant developmental delays, residual neurologic impairments, and seizure disorders. The degree of neurologic impairment in urea cycle disorders has been shown to correlate with peak levels of ammonia and the duration of hyperammonemic coma. Late-onset NAGS deficiency has a variable age of onset, and the degree of residual enzyme activity is heterogeneous.

Clinical Efficacy

In the pivotal trial evaluating Carbaglu, all patients had NAGS gene mutations by DNA testing with elevation of baseline ammonia levels prior to initial dose of Carbaglu (range, 72 to 1,428 µmol/L [normal range, 5 to 50 µmol/L]).[1] By Day 3, the mean ammonia level decreased below 50 µmol/L and remained in this range with long-term treatment.

Safety

Carbaglu has a Warning/Precaution for hyperammonemia. Any episode of acute, severe symptomatic hyperammonemia should be treated as a life-threatening emergency. Treatment of severe hyperammonemia may require dialysis, preferably hemodialysis and/or hemofiltration, to reduce plasma ammonia concentration. Untreated hyperammonemia can result in brain damage and death, and prompt use of all therapies necessary to reduce plasma ammonia level is essential.

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

123. N-Acetylglutamate Synthase (NAGS) 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 (NAGS); 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).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Carbaglu 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.

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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PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Cystaran (cysteamine 0.44% ophthalmic solution – Leadiant Biosciences)

REVIEW DATE: 03/11/2020

OVERVIEW
Cystaran is a cystine-depleting agent indicated for the treatment of corneal cystine crystal accumulation in patients with cystinosis.[1] The recommended dose is one drop into each every waking hour.

Disease Overview
Cystinosis is a rare autosomal recessive inborn error of metabolism in which the transport of cystine out of lysosomes is abnormal.[2-4] 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.[5] Cystaran is the only approved treatment for corneal cystine crystal accumulation. 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 Cystaran. All approvals are provided for the duration noted below. If prescriber specialty is required, add support for this to policy statement. For example: Because of the specialized skills required for evaluation and diagnosis of patients treated with Cystaran as well as the monitoring required for adverse events and long-term efficacy, approval requires Cystaran to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

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

FDA-Approved Indications

124. 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

Cystaran 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.

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

REFERENCES

460. Cystaran [prescribing information]. Gaithersburg, MD: Leadiant Biosciences; May 2018.
461. Wilmer MJ, Schoeber JP, van den Heuvel LP, Levtchenko EN. Cystinosis: practical tools for diagnosis and treatment. *Pediatr Nephrol*. 2011; 26(2): 205–215.
462. 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.
463. Gahl WA, Thoene JG, Schneider JA, et al. NIH Conference. Cystinosis: progress in a prototypic disease. *Ann Int Med*. 1988;109:557-569.
464. 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.

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

125. 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.

119. Concomitant Therapy with Cystagon and Procysbi. There are no data available to support concomitant use.

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

465. Procysbi [prescribing information]. Lake Forest, IL: Horizon Pharma; May 2019.
466. Cystagon [prescribing information]. Morgantown, WV: Mylan Pharmaceuticals, Inc.; January 2019.
467. Wilmer MJ, Schoeber JP, van den Heuvel LP, Levtchenko EN. Cystinosis: practical tools for diagnosis and treatment. *Pediatr Nephrol*. 2011; 26(2): 205–215.
468. 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.
469. Gahl WA, Thoene JG, Schneider JA, et al. NIH Conference. Cystinosis: progress in a prototypic disease. *Ann Int Med*. 1988;109:557-569.
470. National Organization for Rare Disorders (NORD). Cystinosis. Accessed on February 25, 2020. Available at: https://rarediseases.org/rare-diseases/cystinosis/.

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Dojolvi Prior Authorization Policy

- Dojolvi™ (triheptanoin oral liquid – Ultragenyx)

REVIEW DATE: 07/22/2020

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

126. Long-Chain Fatty Acid Oxidation Disorders. Approve for 1 year if the patient meets the following criteria (A, B, and C):

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) 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:

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

471. Dojolvi™ [prescribing information]. Novato, CA: Ultragenyx; June 2020.
472. Merritt JL II, Norris M, Kanungo S. Fatty acid oxidation disorders. *Ann Transl Med.* 2018;6(24):473.
473. Knotterus SJG, Bleeker JC, Wüst RCI, et al. Disorders of mitochondrial long-chain fatty acid oxidation and the carnitine shuffle. *Rev Endocr Metab Disord.* 2018;19:93-106.
474. 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.
475. 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.
476. 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.

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: 10/09/2019

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

127. 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.** The 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)** The 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

Nitisinone 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.

122. 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.

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

477. Orfadin [prescribing information]. Waltham, MA: Sobi, Inc.; May 2019.
478. Nityr [prescribing information]. Cambridge, UK: Cycle Pharmaceuticals; November 2018.
479. 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.
480. National Organization for Rare Disorders. Tyrosinemia type 1. Accessed on October 2, 2019. Available at: https://rarediseases.org/rare-diseases/tyrosinemia-type-1/.

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

128. 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.

124. Concomitant Therapy with Buphenyl and Ravicti. There are no data available to support concomitant use.

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

REFERENCES

481. Buphenyl [prescribing information]. Lake Forest, IL: Horizon Pharma; November 2018.
482. Ravicti [prescribing information]. Lake Forest, IL: Horizon Pharma; October 2019.
483. 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.
484. 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.
485. 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.
486. National Organization for Rare Disorders (NORD). Urea cycle disorders. Accessed on February 25, 2020. Available at: https://rarediseases.org/physician-guide/urea-cycle-disorders/.

PRIOR AUTHORIZATION POLICY

POLICY: Metabolic Disorders – Tiopronin Products
- Thiola® (tiopronin tablets – Mission Pharmacal)
- Thiola® EC (tiopronin delayed-release tablets – Mission Pharmacal)

REVIEW DATE: 09/18/2019

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). 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
Tiopronin 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.)

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
111. Thiola® [prescribing information]. San Antonio, TX: Mission Pharmacal; June 2019.
112. Thiola® EC [prescribing information]. San Antonio, TX: Mission Pharmacal; June 2019.
113. Cystinuria. National Organization for Rare Disorders. Updated 2017. Available at: https://rarediseases.org/rare-diseases/cystinuria/. Accessed on July 9, 2019.
114. Castro Pereira DJ, Schoolwerth AC, Pais VM. Cystinuria: current concepts and future directions. *Clin Nephrology*. 2015;83(3):138-146.
115. 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 July 9, 2019.

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
116. Xuriden® oral granules [prescribing information]. Rockville, MD: Wellstat Therapeutics; December 2019.
117. 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.
118. 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.

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.

254. 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

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

129. 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.

126. 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. Nurtec ODT [prescribing information]. New Haven, CT: Biohaven Pharmaceuticals; February 2020.
488. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629-808.
489. MacGregor EA. In the clinic. Migraine. *Ann Intern Med*. 2017;166(7):ITC49-ITC64.
490. Lipton RB, Silberstein SD. Episodic and chronic migraine headache: breaking down barriers to optimal treatment and prevention. *Headache*. 2015;52:103-122.

491. American Headache Society. The American Headache Society position statement on integrating new migraine treatments into clinical practice. *Headache*. 2019;59:1-18.

PRIOR AUTHORIZATION POLICY

POLICY: Migraine – Reyvow™ (lasmiditan tablet – Lilly)

DATE REVIEWED: 12/18/2019; selected revision 06/03/2020

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] The 5-HT_{1F} receptor subtype is located in the trigeminal ganglion, the trigeminal nucleus caudalis, and cephalic blood vessels. 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 precise mechanism of action of Reyvow for the treatment of migraine headache is unknown.[1] The recommended dose is 50 mg, 100 mg, or 200 mg as needed with or without food. 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] Migraine headache episodes typically last 4 to 72 hours, if untreated. Migraine affects approximately 15% of US adults.[6] 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.[5] Episodic migraine is characterized by headaches that occur < 15 days/month.[7] 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).[8] Treat at the first sign of pain to improve the probability of achieving freedom from pain and reduce attack-related disability.

Safety

Reyvow may cause significant driving impairment.[1] Patients should not engage in potentially hazardous activities requiring complete mental alertness, such as driving a motor vehicle or operating machinery, for at least 8 hours after each dose of Reyvow, and those who cannot follow this advice should not take Reyvow. In a study of healthy volunteers, driving performance was assessed at 90 minutes after administration of Reyvow 50 mg, 100 mg, 200 mg,

alprazolam 1 mg, and placebo in a randomized, double-blind, placebo- and active-controlled, five-period crossover study using a computer-based driving simulation (n = 90). Driving performance was evaluated using a validated threshold established in a population with blood alcohol concentration of 0.05%. The primary outcome measure was the difference from placebo in the standard deviation of lateral position (SDLP), a measure of driving performance. All doses of Reyvow exhibited a dose-dependent impairment of simulated driving performance at 90 minutes after administration. In a separate randomized, double-blind, placebo- and active-controlled, four-period crossover study in healthy volunteers, driving performance was assessed at 8, 12, and 24 hours after administration of Reyvow 100 mg or 200 mg, using diphenhydramine 50 mg as the control (n = 67). The study evaluated computer-based simulated driving performance with the primary endpoint of SDLP. The mean SDLP did not reach the threshold for driving impairment at ≥ 8 hours after administration of Reyvow 100 or 200 mg.

Reyvow may also cause CNS depression, including dizziness and sedation, and should be used with caution if used in combination with alcohol or other CNS depressants.[1] In controlled clinical trials, dizziness and increased systolic blood pressure occurred more frequently in patients who were ≥ 65 years of age compared with patients who were < 65 years of age. In general, dose selection for an elderly patient should be cautious, starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

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

130. 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

Reyvow 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.)

127. 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. Reyvow® tablets [prescribing information]. Indianapolis, IN: Lilly USA, LLC; October 2019.
493. Do TP, Guo S, Ashina M. Therapeutic novelties in migraine: new drugs, new hope? *J Headache Pain*. 2019;20(1):37.
494. Kuca B, Silberstein SD, Wietecha L, et al. Lasmiditan is an effective acute treatment for migraine. *Neurology*. 2018;91:e2222-e2232.
495. 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.
496. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629-808.
497. MacGregor EA. In the clinic. Migraine. *Ann Intern Med*. 2017;166(7):ITC49-ITC64.
498. Lipton RB, Silberstein SD. Episodic and chronic migraine headache: breaking down barriers to optimal treatment and prevention. *Headache*. 2015;52:103-122.
499. American Headache Society. The American Headache Society position statement on integrating new migraine treatments into clinical practice. *Headache*. 2019;59:1-18.

PRIOR AUTHORIZATION POLICY

POLICY: Migraine – Ubrelvy™ (ubrogepant tablet – Allergan)

DATE REVIEWED: 01/29/2020; selected revision 06/03/2020

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. The recommended dose of Ubrelvy is 50 mg or 100 mg taken orally with or without food. If needed, a second dose may be taken ≥ 2 hours after the initial dose. The maximum dose in a 24-hour period is 200 mg. The safety of treating more than 8 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 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

131. 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

Ubrelvy 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.

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

REFERENCES

500. Ubrelvy™ tablets [prescribing information]. Madison, NJ: Allergan; December 2019.
501. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). *Cephalalgia*. 2013;33:629-808.
502. MacGregor EA. In the clinic. Migraine. *Ann Intern Med*. 2017;166(7):ITC49-ITC64.
503. Lipton RB, Silberstein SD. Episodic and chronic migraine headache: breaking down barriers to optimal treatment and prevention. *Headache*. 2015;52:103-122.
504. American Headache Society. The American Headache Society position statement on integrating new migraine treatments into clinical practice. *Headache*. 2019;59:1-18.

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Ampyra® (dalfampridine extended-release tablets – Acorda Therapeutics, generic)

REVIEW DATE: 10/02/2019

OVERVIEW

Ampyra is a potassium channel blocker that is indicated to improve walking in adult patients 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] The risk of seizures in those with mild renal impairment (estimated CrCl between 50 to 80 mL/min) is unknown, but the plasma levels of Ampyra in such patients may approach those noted at a dose of 15 mg twice daily (BID), a dose related to an increase risk of seizures. Of note, the maximum recommended Ampyra dose is 10 mg BID. Also, Ampyra should not be taken with other forms of 4-aminopyridine (4-AP, fampridine), which is an immediate-release agent that sometimes is compounded, because the active ingredients are similar. The most common adverse events noted with Ampyra (incidence ≥ 2% and at a rate greater than placebo) were urinary tract infection, insomnia, dizziness, headache, nausea, asthenia, back pain, balance disorder, MS relapse, paresthesia, nasopharyngitis, constipation, dyspepsia, and pharyngolaryngeal pain. The safety and effectiveness in children aged < 18 years have not been established.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Ampyra. 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. All approvals are provided for 1 year in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

37. Multiple Sclerosis (MS). Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Ampyra is being used to improve mobility in a patient with MS; AND
- **B)** Ampyra is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of MS.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Ampyra 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.)

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
34. Ampyra® extended-release tablets [prescribing information]. Ardsley, NY: Acorda Therapeutics, Inc.; September 2017.

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Aubagio Prior Authorization Policy
- Aubagio® (teriflunomide tablets – Genzyme/Sanofi)

REVIEW DATE: 08/05/2020

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)** The patient has a relapsing form of multiple sclerosis; AND
   - **B)** The agent 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:

256. 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), 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 MS agents in combination is safe provides added efficacy.

257. 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]

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

119. Aubagio® tablets [prescribing information]. Cambridge, MA: Genzyme Corporation (a Sanofi company); February 2020.
120. 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.
121. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
122. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Avonex Prior Authorization Policy

- Avonex® (interferon beta-1a injection for intramuscular use – Biogen)

REVIEW DATE: 08/05/2020

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) The patient has a relapsing form of multiple sclerosis; AND
   S) The agent 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), 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 MS agents in combination is safe 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.

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

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)** The patient has a relapsing form of multiple sclerosis; AND
   - **B)** The agent 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:

259. 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), and Zeposia® (ozanimod capsules).[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 provides added efficacy.

260. 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]

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

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124. 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 July 31, 2020.

125. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
126. 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.

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

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) The patient has a relapsing form of multiple sclerosis; AND
   B) The agent 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), and Lemtrada® (alemtuzumab injection for intravenous 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 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 July 31, 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.

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Gilenya Prior Authorization Policy
- Gilenya® (fingolimod capsules – Novartis)

REVIEW DATE: 08/05/2020

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)** The patient has a relapsing form of multiple sclerosis; AND
   - **B)** The agent 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:

262. 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), 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.

263. 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]

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

127. Gilenya® capsules [prescribing information]. East Hanover, NJ: Novartis; December 2019.
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132. Lublin F, Miller DH, Freedman MS, et al, on behalf of the INFORMS Study Investigators. Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomized, double-blind, placebo-controlled trial. *Lancet*. 2016;387:1075-1084.

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

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) The patient has a relapsing form of multiple sclerosis; AND
   U) The 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), 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.

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.

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23. Glatopa® injection for subcutaneous use [prescribing information]. Princeton, NJ: Sandoz; January 2020.
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25. Glatiramer acetate injection 40 mg/mL [prescribing information]. Morgantown, WV: Mylan Pharmaceuticals; February 2020.
26. 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.
27. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
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.

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

132. 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:

265. 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.

266. 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]

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
505. Kesimpta® injection for subcutaneous use [prescribing information]. East Hanover, NJ: Novartis Pharmaceutical Corporation; August 2020.
506. 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 August 23, 2020.
507. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
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PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Lemtrada® (alemtuzumab injection for intravenous use)

DATE REVIEWED: 11/13/2019

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] 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. Limitations of Use. Lemtrada is not recommended for use in patients with clinically isolated syndrome because of its safety profile. The recommended dose of Lemtrada is 12 mg/day given by intravenous (IV) infusion for two treatment courses. The first treatment course is 12 mg/day IV on 5 consecutive days (60 mg total dose) and the second treatment course is 12 mg/day IV on 3 consecutive days (36 mg total dose) given 12 months after the first treatment course. Following the second treatment course, subsequent treatment courses of 12 mg per day on 3 consecutive days (36 mg total dose) may be given, as needed, at least 12 months after the last dose of any prior treatment course. Infuse Lemtrada over 4 hours and administer the agent in a setting that has equipment and personnel to appropriately manage anaphylaxis or serious infusion reactions.[1] Lemtrada contains the same active ingredient found in Campath® (alemtuzumab injection for IV use), which is FDA-approved for the treatment of B-cell chronic lymphocytic leukemia.[6]

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.

Many disease-modifying MS agents are FDA-approved for use in patients with relapsing forms of MS.[2] Options include self-administered injectable agents (e.g., glatiramer acetate products and interferon beta agents), oral agents (i.e., Tecfidera® [dimethyl fumarate delayed-release capsules], Gilenya® [fingolimod capsules], Mayzent® [siponimod tablets]), Aubagio® [teriflunomide tablets], Mavenclad® [cladribine tablets], Vumerity™ [diroximel fumarate delayed-release capsules]), and intravenously infused agents (i.e., Tysabri® [natalizumab injection for intravenous use], Ocrevus® [ocrelizumab injection for intravenous use], and mitoxantrone injection for intravenous use). Ocrevus is the only agent FDA-approved for primary progressive MS.

Guidelines

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] Some program requirements include that prescribers must be certified with the program by enrolling and completing training. Also, patients must enroll in the program and comply with ongoing monitoring requirements. Pharmacies are required to be certified with the program and must only dispense Lemtrada to certified healthcare facilities that are authorized to receive Lemtrada. It is required that healthcare facilities enroll in the program and verify that patients are authorized before infusing Lemtrada. Healthcare facilities must have on-site access to equipment and personnel trained to manage infusion reactions.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Lemtrada injection. 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. All approvals are noted for the durations below.

Automation: None.

Documentation: In the *Multiple Sclerosis – Lemtrada 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 magnetic resonance imaging (MRI) reports.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

1. **Multiple Sclerosis (MS).** Approve for the duration of therapy noted if the patient meets one of the following criteria (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.** The patient is ≥ 17 years of age; AND
     - **ii.** The patient has a relapsing form of MS; AND
     - **iii.** Lemtrada is prescribing by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; AND
     - **iv.** The patient meets one of the following (a or b):
       - **a)** According to the prescriber the patient has had an inadequate response or is unable to tolerate two disease-modifying agents used for MS; OR Note: Examples include Avonex, Rebif, Betaseron, Extavia, Copaxone, Plegridy, Gilenya, Glatopa, glatiramer acetate injection, Aubagio, Tecfidera, Mavenclad, Mayzent, Vumerity, Tysabri, or Ocrevus); OR
       - **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. The 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]**; OR
   - **B)** Patient Who Has Completed a Previous Lemtrada Therapy Course. Approve for 3 days in patients who meet all of the following criteria (i, ii, iii and iv):
     - **i.** The patient is ≥ 17 years of age; AND
     - **ii.** The patient has a relapsing form of MS; AND
     - **iii.** Lemtrada is prescribed by or in consultation with a neurologist or a physician that specializes in the treatment of MS; AND
     - **iv.** At least 12 months has elapsed from the last dose of any prior Lemtrada treatment course.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Lemtrada 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 Other Disease-Modifying Agents Used for Multiple Sclerosis (MS).** Note: Examples of disease-modifying agents used for MS include Betaseron®/Extavia® (interferon beta-1b injection), Rebif® (interferon beta-1a injection [subcutaneous]), Copaxone®/Glatopa® (glatiramer acetate injection), glatiramer acetate injection, Avonex® (interferon beta-1a injection [intramuscular]), Plegridy® (peginterferon beta-1a injection), Gilenya® (fingolimod tablets), Aubagio® (teriflunomide

tablets), Mavenclad® (cladribine tablets), Mayzent® (siponimod tablets), Tecfidera® (dimethyl fumarate delayed-release capsules), Vumerity™ (diroximel fumarate delayed-release capsules), Tysabri® (natalizumab injection for intravenous use), and Ocrevus® (ocrelizumab injection for intravenous use). Lemtrada should not be given in combination with other disease-modifying agents used for MS. Concomitant use of Lemtrada with immunosuppressive therapies could increase the risk of immunosuppression.[1]

2. **Human Immunodeficiency Virus (HIV) Infection (Patients With).** Use of Lemtrada is contraindicated in patients who are infected with HIV because Lemtrada causes prolonged reductions of CD4+ lymphocyte counts.[1]

3. **Non-Relapsing Forms of Multiple Sclerosis.** Note: An example of a non-relapsing form of MS is primary progressive MS. The efficacy of Lemtrada has not been established in patients with MS with non-relapsing forms of the disease.[1]

4. **Clinically Isolated Syndrome.** Lemtrada is not recommended for use in patients with clinically isolated syndrome due to its safety profile.[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

236. Lemtrada® injection for intravenous use [prescribing information]. Cambridge, MA: Genzyme Corporation; October 2019.
237. 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 7, 2019.
238. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
239. 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.
240. 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.
241. Campath® injection for intravenous use [prescribing information]. Cambridge, MA: Genzyme; November 2018.

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Mavenclad Prior Authorization Policy
- Mavenclad® (cladribine tablets – EMD Serono)

REVIEW DATE: 08/05/2020

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)** The patient has a relapsing form of multiple sclerosis; AND
- **D)** The agent 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:

268. Clinically Isolated Syndrome. Mavenclad is not recommended for use in patients with clinically isolated syndrome due to its safety profile.[1]

269. 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), 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.

270. 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]

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

242. Mavenclad® tablets [prescribing information]. Rockland, MA: EMD Serono; April 2019.
243. 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.

244. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
245. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Mayzent Prior Authorization Policy
- Mayzent® (siponimod tablets – Novartis)

REVIEW DATE: 08/05/2020

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 AEs 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)** The patient has a relapsing form of multiple sclerosis; AND
- **B)** The agent 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:

272. 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), 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.

273. 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]

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

246. Mayzent™ tablets [prescribing information]. East Hanover, NJ: Novartis; March 2019.
247. 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.
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PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Ocrevus® (ocrelizumab injection for intravenous use – Genentech/Roche)

DATE REVIEWED: 11/13/2019

OVERVIEW

Ocrevus is a CD20-directed cytolytic antibody indicated for the treatment of relapsing forms of multiple sclerosis (MS) to include clinically isolated syndrome, relapsing remitting MS, and active secondary progressive MS in adults.[1] Ocrevus is also indicated for primary progressive MS in adults. Ocrevus is the only MS medication indicated for use in primary progressive MS.

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. Table 1 provides a comparison between relapsing MS and primary progressive MS.

Table 1. Relapsing MS vs. Primary Progressive MS.[2,5]

Characteristic	Relapsing MS	Primary Progressive MS
Percentage of the MS population	85% to 90%	10% to 15%
Clinical course	Recurrent subacute events of neurological dysfunction followed by complete or partial recovery.	Worsening of neurological dysfunction at disease onset with little or no recovery.
Age at onset	30 years of age	40 years of age
Gender	2:1 ratio of females to males	1:1 ratio of females to males
Disability prognosis	Generally can occur after many years.	Rapid progression of disability.
Inflammation/brain lesions	There is less inflammation with primary progressive MS. Also, patients with primary progressive MS have fewer brain lesions vs. relapsing MS and the lesions tend to contain fewer inflammatory cells.	
Systems impacted	Patients with primary progressive MS have relatively more issues with ambulation compared to patients with relapsing forms of MS.	

MS – Multiple sclerosis.

Many disease-modifying MS agents are FDA-approved for use in patients with relapsing forms of MS.[2] Options include self-administered injectable agents (e.g., glatiramer acetate products, and interferon beta agents), oral agents (i.e., Tecfidera® [dimethyl fumarate delayed-release capsules], Gilenya® [fingolimod capsules], Mayzent® [siponimod tablets]), Aubagio® [teriflunomide tablets], Mavenclad® [cladribine tablets], Vumerity™ [diroximel fumarate delayed-release capsules]), and intravenously infused agents (i.e., Tysabri® [natalizumab injection for intravenous use], Lemtrada® [alemtuzumab injection for intravenous use], and mitoxantrone injection for intravenous use). No other therapies, besides Ocrevus, are FDA-approved for primary progressive 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 (AEs) and long-term efficacy, approval requires Ocrevus to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

2. Multiple Sclerosis (MS), Relapsing Forms. Approve for 1 year if the patient meets all of the following criteria (A, B, and C):
- **E)** The patient is ≥ 18 years of age; AND
- **F)** The patient has a relapsing form of multiple sclerosis (MS); AND
- **G)** Ocrevus is prescribed by or in consultation with a physician who specializes in the treatment of MS and/or a neurologist.

30. Multiple Sclerosis (MS), Primary Progressive. Approve for 1 year if the patient meets all of the following criteria (A and B).
- **74.** The patient is ≥ 18 years of age; AND
- **75.** Ocrevus 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

Ocrevus 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.

275. Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis (MS). 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), Copaxone®/Glatopa® (glatiramer acetate injection), glatiramer acetate injection, Gilenya® (fingolimod tablets), Aubagio® (teriflunomide tablets), Tecfidera® (dimethyl fumarate delayed-release capsules), Tysabri® (natalizumab injection for intravenous use), Mayzent® (siponimod tablets), Mavenclad® (cladribine tablets), Vumerity™ (diroximel fumarate delayed-release capsules), and Lemtrada® (alemtuzumab injection for intravenous use). The concomitant use of Ocrevus with other immune-modulating or immunosuppressive therapies is anticipated to increase the risk of immunosuppression.[1] Ocrevus is not indicated for use in combination with other MS disease-modifying therapies and the safety and efficacy have not been adequately established.

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

225. Ocrevus® injection for intravenous infusion [prescribing information]. San Francisco, CA: Genentech, Inc (a Member of the Roche Group); July 2019.
226. 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 7, 2019.
227. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
228. 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.
229. Gajofatto A, Turatti M, Benedetti MD. Primary progressive multiple sclerosis: current therapeutic strategies and future perspectives. *Expert Rev Neurother*. 2017;17(4):393-406.

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Plegridy Prior Authorization Policy

- Plegridy® (peginterferon beta-1a injection [subcutaneous] – Biogen Idec)

REVIEW DATE: 08/05/2020

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 (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 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)** The patient has a relapsing form of multiple sclerosis; AND
   - **W)** The 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), 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.

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 use [prescribing information]. Cambridge, MA: Biogen, Idec; March 2020.
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 July 31, 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.

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Rebif Prior Authorization Policy
- Rebif® (interferon beta-1a injection for subcutaneous use – EMD Serono)

REVIEW DATE: 08/05/2020

OVERVIEW
Rebif is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to include clinically isolated syndrome, relapsing remising 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 Rebif. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Rebif as well as the monitoring required for adverse events and long-term efficacy, approval requires Rebif to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rebif 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)** The patient has a relapsing form of multiple sclerosis; AND
   - **B)** The medication is prescribed by or after consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage is Rebif 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), 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), 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.

35. Non-Relapsing Forms of Multiple Sclerosis.
Note: An example of a non-relapsing form of multiple sclerosis (MS) is primary progressive MS. The efficacy of Rebif has not been established in patients with MS with non-relapsing forms of MS.[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. Rebif® injection for subcutaneous use [prescribing information]. Rockland, MD: EMD Serono; June 2020.
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 July 31, 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.

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Tecfidera Prior Authorization Policy

- Tecfidera® (dimethyl fumarate delayed-release capsules – Biogen)

REVIEW DATE: 08/05/2020

OVERVIEW

Tecfidera 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 Tecfidera, including a fatal case.[1]

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

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Tecfidera 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) The patient has a relapsing form of multiple sclerosis; AND
   D) The agent 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 Tecfidera is not recommended in the following situations:

277. **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), 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.

278. **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 Tecfidera has not been established in patients with multiple sclerosis with non-relapsing forms of multiple sclerosis.[1]

279. 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. Tecfidera® delayed-release capsules [prescribing information]. Cambridge, MA: Biogen; February 2020.
134. 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.
135. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
136. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Vumerity Prior Authorization Policy
- Vumerity® (diroximel fumarate delayed-release capsules – Biogen/Alkermes)

REVIEW DATE: 08/05/2020

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 Tecfidera® (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)** The patient has a relapsing form of multiple sclerosis; AND
   - **F)** The agent 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:

280. 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), 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.

281. 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]

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
137. Vumerity® delayed-release capsules [prescribing information]. Cambridge, MA and Waltham, MA: Biogen and Alkermes; March 2020.
138. 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.
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PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis – Zeposia Prior Authorization Policy
- Zeposia® (ozanimod capsules – Celegene)

REVIEW DATE: 08/05/2020

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)** The patient has a relapsing form of multiple sclerosis; AND
- **B)** The agent 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:

283. 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), 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.

284. 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]

285. 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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PRIOR AUTHORIZATION POLICY

POLICY: Multiple Sclerosis and Crohn's Disease – Tysabri® (natalizumab injection for intravenous use – Biogen)

DATE REVIEWED: 11/13/2019

OVERVIEW

Tysabri, an integrin receptor antagonist, 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] Tysabri increases the risk of progressive multifocal leukoencephalopathy (PML). When initiating and continuing treatment with Tysabri physicians should consider whether the expected benefit of Tysabri is sufficient to offset the risks. Tysabri is also indicated for inducing and maintaining clinical response and remission in adults with moderately to severely active Crohn's 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.[1] Tysabri should not be used in combination with immunosuppressants (e.g., azathioprine, 6-mercaptopurine, cyclosporine, methotrexate) or inhibitors of TNFα. For both indications, the recommended dose of Tysabri is 300 mg by intravenous infusion over approximately 1 hour once every 4 weeks.[1]

Disease Overview

Multiple Sclerosis (MS)

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.

Many disease-modifying MS agents are FDA-approved for use in patients with relapsing forms of MS.[2] Options include self-administered injectable agents (e.g., glatiramer acetate products, and interferon beta agents), oral agents (i.e., Tecfidera® [dimethyl fumarate delayed-release capsules], Gilenya® [fingolimod capsules], Mayzent® [siponimod tablets]), Aubagio® [teriflunomide tablets], Mavenclad® [cladribine tablets], Vumerity™ [diroximel fumarate delayed-release capsules]), and intravenously infused agents (i.e., Lemtrada® [alemtuzumab injection for intravenous use], Ocrevus® [ocrelizumab injection for intravenous use], and mitoxantrone injection for intravenous use).

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]

The American College of Gastroenterology (ACG) has guidelines on management of Crohn's disease in adults (2018).[7] Some of the recommendations are summarized for moderate to severe disease or moderate to high-risk disease. Oral corticosteroids are effective and can be used short-term to alleviate signs and

symptoms of moderately to severely active Crohn's disease. Thiopurines (azathiopurine, 6-mercaptopurine) are effective and should be considered for use for steroid-sparing Crohn's disease. Azathioprine and 6-mercaptopurine are effective therapies and should be considered for patients with Crohn's disease for maintenance of remission. 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. Anti-TNF agents should be given for Crohn's disease refractory to 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, which requires registration by the prescribers, patients, infusion centers, and pharmacies associated with infusion centers.[1] Tysabri must be administered only to patients enrolled in and who meet all the conditions of the TOUCH Prescribing Program.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Tysabri injection. 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. Approvals for multiple sclerosis are provided for 1 year in duration. Approvals for Crohn's disease are for an initial 3-month approval duration (where 1 month is equal to 30 days), and then for a 1 year approval for patients currently receiving Tysabri.

Automation: None.

Documentation: In the *Multiple Sclerosis – Tysabri Prior Authorization Policy*, documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and magnetic resonance imaging (MRI) reports.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

1. **Multiple Sclerosis (MS).** 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.** The patient is ≥ 18 years of age; AND
- **ii.** The patient has a relapsing form of multiple sclerosis (MS); AND
- **iii.** Tysabri is prescribed by or in consultation with a physician who specializes in the treatment of multiple sclerosis (MS) and/or a neurologist; AND
- **iv.** The patient meets one of the following (a or b):
  - **a)** According to the prescriber the patient has had an inadequate response or is unable to tolerate one disease-modifying agent used for MS. Note: Examples of disease-modifying agents for multiple sclerosis include Avonex (interferon beta-1a for intramuscular [IM] injection), Rebif [interferon beta-1a for subcutaneous [SC] injection), Betaseron (interferon beta-1b for SC injection), Extavia (interferon beta-1b for SC injection), Copaxone/Glatopa (glatiramer acetate injection for SC use), glatiramer acetate injection, Plegridy (peginterferon beta-1a SC injection), Gilenya (fingolimod capsules), Aubagio (teriflunomide tablets), Tecfidera (dimethyl fumarate delayed-release capsules), Mavenclad (cladribine tablets), Mayzent (siponimod tablets), Vumerity™ (diroximel fumarate delayed-release capsules), Lemtrada® (alemtuzumab injection for intravenous use), and Ocrevus® (ocrelizumab injection for intravenous); OR
  - **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.** The 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]**; OR

B) Patients currently receiving Tysabri. 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 has a relapsing form of multiple sclerosis; AND
- **iii.** Tysabri is prescribed by or in consultation with a physician who specializes in the treatment of MS 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.** The patient is ≥ 18 years of age; AND
- **ii.** The patient has moderately to severely active Crohn's disease; AND
- **iii.** Tysabri is prescribed by or in consultation with a gastroenterologist; AND
- **iv.** The patient has tried at least two biologics for Crohn's disease; 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); OR

B) For patients currently receiving Tysabri. 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 has had a response (e.g., reduced number of liquid/soft stools, reduced abdominal pain, less use of antidiarrheal agents) as determined by the prescriber; AND
- **iii.** Tysabri is prescribed by or in consultation with a gastroenterologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Tysabri 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 an Immunosuppressant Agent in Patients with Crohn's Disease.** Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, methotrexate, an infliximab product, an adalimumab product, Cimzia, Entyvio and Stelara. 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]

2. **Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis (MS).** 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), glatiramer acetate injection, Avonex® (interferon beta-1a injection [intramuscular]), Lemtrada® (alemtuzumab injection for intravenous use), Plegridy® (peginterferon beta-1a injection), Gilenya® (fingolimod tablets), Aubagio® (teriflunomide tablets), Tecfidera® (dimethyl fumarate delayed-release capsules), Vumerity™ (diroximel fumarate delayed-release capsules), Mayzent® (siponimod tablets), Mavenclad® (cladribine tablets), and Ocrevus® (ocrelizumab injection for intravenous use). Tysabri is only indicated as monotherapy due to an increased risk of PML.[1]

3. **Non-Relapsing Forms of Multiple Sclerosis.** Note: An example of a non-relapsing form of multiple sclerosis (MS) is primary progressive MS. The safety and efficacy of Tysabri have not been established in patients with primary progressive MS.

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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PRIOR AUTHORIZATION POLICY

POLICY: Muscular Dystrophy – Emflaza™ (deflazacort tablets and oral suspension – PTC Therapeutics, Inc.)

DATE REVIEWED: 3/11/2020

OVERVIEW

Emflaza is a corticosteroid indicated for the treatment of patients 2 years of age and older with Duchenne muscular dystrophy (DMD).[1] The efficacy and safety of Emflaza have not been established in patients < 2 years of age. The Emflaza oral suspension contains benzyl alcohol as a preservative and therefore carries a warning about the risk of gasping syndrome which can occur in neonates and low birth weight infants.

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. 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. All approvals are provided for 1 year.

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 Emflaza is recommended in those who meet the following criteria:

FDA-Approved Indications

31. Duchenne Muscular Dystrophy (DMD). Approve for 1 year if the patient meets ALL of the following criteria (A, B, and C):

- **A)** The patient is 2 years of age and older; AND
- **B)** The patient meets ONE of the following conditions (i or ii):
  - **i.** The patient has tried prednisone 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) [a, b, c, or d]:
    - **a)** Cushingoid appearance **[documentation required]**; OR
    - **b)** Central (truncal) obesity **[documentation required]**; OR
    - **c)** Undesirable weight gain defined as ≥ 10% of body weight gain increase over a 6-month period **[documentation required]**; OR
    - **d)** Diabetes and/or hypertension that is difficult to manage according to the prescribing physician] **[documentation required]**.
  - **ii.** According to the prescriber, the patient has experienced a severe behavioral adverse event (AE) while on prednisone therapy that has or would require a prednisone dose reduction **[documentation required]**.
- **C)** The medication is prescribed by or in consultation with a physician who specializes in the treatment of Duchenne muscular dystrophy (DMD) and/or neuromuscular disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Emflaza 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.

286. 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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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.

1. **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%.

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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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:

3. **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.

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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PRIOR AUTHORIZATION POLICY

POLICY: Muscular Dystrophy – Vyondys 53 (golodirsen intravenous infusion – Sarepta)

REVIEW DATE: 12/13/2019

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.

5. **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.

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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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

32. 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.)

287. Acute Post-Surgical Hypoparathyroidism. Natpara was only studied in patients with chronic hypoparathyroidism.

288. Hypoparathyroidism Caused by Calcium-Sensing Receptor Mutations. Natpara was not studied in this patient population.

289. 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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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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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.)

290. **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.

291. **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.

292. **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.

293. **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.

294. **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.

295. 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.

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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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

133. 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:

129. 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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PRIOR AUTHORIZATION POLICY

POLICY: Northera® (droxidopa capsules – Chelsea Therapeutics)

DATE REVIEWED: 11/20/2019

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. The mechanism of action of Northera is unknown. Northera is a synthetic amino acid analog that is metabolized to norepinephrine by dopa-decarboxylase, which is found throughout the body. Northera is thought to exert its effects through norepinephrine, which increases blood pressure (BP) by inducing peripheral arterial and venous vasoconstriction. 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.

Disease Overview

OH is a sustained reduction in SBP of at least 20 mmHg or DBP of 10 mmHg within 3 minutes of standing or head-up tilt to at least 60° on a tilt table.[2] OH is caused by an excessive fall in a patient's cardiac output or by defective or inadequate vasoconstrictor mechanisms. 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. Patients with autonomic failure and the elderly are also susceptible to significant decreases in BP associated with meals. This may be exacerbated by large meals, meals high in carbohydrates, and alcohol intake. 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] A variety of nonpharmacologic approaches have been used to treat symptoms of NOH, including arising slowly, elevating the head of the bed, and/or wearing elastic stockings.[6] Spreading total daily carbohydrate intake to multiple smaller meals has been shown to decrease OH symptoms.[7] Adequate salt and fluid intake may be useful (e.g., dietary sodium intake of at least 10 g/day and fluid intake of greater than 2 L/day) in patients without concomitant renal dysfunction.[6] These nonpharmacologic interventions should be considered first in the treatment of NOH. 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]

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, initial 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:

Food and Drug Administration (FDA)-Approved Indications

76. 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) Northera has been prescribed by or in consultation with a cardiologist or a neurologist; AND
d) Patient has tried two other medications (e.g., fludrocortisone, desmopressin, dihydroergotamine, indomethacin, pyridostigmine, erythropoietin, midodrine); AND
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

Northera 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.)

297. 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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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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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Abiraterone Acetate (Zytiga® tablets – Janssen Biotech Inc.; generics [250 mg tablets only])

DATE REVIEWED: 02/19/2020; selected revision 03/04/2020

OVERVIEW

Abiraterone acetate 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. Abirateone acetate in combination with prednisone is indicated for use for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) and for the treatment of metastatic high-risk castration-sensitive prostate cancer (mCSPC). Inhibition of CYP17 by abiraterone acetate can also result in increased mineralocorticoid production by the adrenal glands; the use of prednisone with abiraterone acetate is to counteract this mineralocorticoid excess.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on prostate cancer (version 4.2019 – August 19, 2019) 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, 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, 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) 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.

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) The 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) 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.

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); OR

ii. Patient has had an orchiectomy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Abiraterone acetate 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.)

298. 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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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Afinitor® (everolimus tablets – Novartis)
Afinitor Disperz® (everolimus tablets for oral suspension – Novartis)
Everolimus tablets 2.5 mg, 5 mg, 7.5 mg (generics – Multiple manufacturers)

DATE REVIEWED: 05/27/2020

OVERVIEW

Afinitor, a kinase inhibitor, is indicated for the following conditions:[1]

1) treatment of postmenopausal women with advanced hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative breast cancer (advanced HR+ breast cancer) in combination with exemestane, after failure of treatment with letrozole or anastrozole;
2) treatment of adult patients with progressive neuroendocrine tumors (NETS) of pancreatic origin (PNET) and adults with progressive, well-differentiated, non-functional NETS of gastrointestinal (GI) 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;
3) treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of treatment with Sutent® (sunitinib capsules) or Nexavar® (sorafenib tablets);
4) treatment of adult patients with renal angiomyolipoma and tuberous sclerosis complex (TSC) not requiring immediate surgery; and
5) treatment of adult patients with TSC who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected.[1]
6) adjunctive treatment of adult and pediatric patients ≥ 2 years of age with TSC-associated partial-onset seizures.

Afinitor 2.5 mg, 5 mg and 7.5 mg are available as generic tablets. Afinitor 10 mg tablets and Afinitor Disperz are only available as brand products.

Afinitor Disperz is indicated for the treatment of adult and pediatric patients aged ≥ 1 years with TSC who have SEGA that requires therapeutic intervention but cannot be curatively resected.[1] Afinitor Disperz is also indicated for the adjunctive treatment of adult and pediatric patients aged ≥ 2 years with TSC-associated partial-onset seizures. 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. 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 3 years in duration. 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 everolimus (Afinitor, generics) 2.5mg, 5 mg, 7.5 mg, Afinitor 10 mg, or Afinitor Disperz is recommended in those who meet the following criteria:

FDA-Approved Indications

33. Breast Cancer. Approve for 3 years if the patient meets the following criteria (A, B, C, D, E, and F):
- **A)** The patient has recurrent or Stage IV, hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND
- **A)** The patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer;; AND
- **B)** The patient has tried at least one prior endocrine therapy (e.g., anastrozole, letrozole, or tamoxifen); AND
- **C)** The patient meets ONE of the following conditions (i or ii):
  - **i.** The patient is a postmenopausal female* or a male*; OR
  - **ii.** The patient is premenopausal or perimenopausal AND is receiving ovarian suppression/ablation[3] with a gonadotropin-releasing hormone (GnRH) agonist (e.g., Lupron® [leuprolide], Trelstar® [triptorelin], Zoladex® (goserelin]), or has had surgical bilateral oophorectomy or ovarian irradiation; AND
- **D)** The 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 (e.g., Lupron [leuprolide], Trelstar [triptorelin], Zoladex (goserelin]); OR
  - **ii.** Afinitor will be used in combination with exemestane, fulvestrant , or tamoxifen; AND

E) The patient has not had disease progression while on Afinitor.

***** Refer to the Policy Statement.

34. Neuroendocrine Tumors of the Pancreas, Gastrointestinal Tract, Lung and Thymus (Carcinoid Tumors) – Advanced, Unresectable, or Metastatic. Approve for 3 years.

35. 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 (e.g., 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) Afinitor 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) The patient has tried imatinib (Gleevec® tablets, generics); AND
B) The patient has tried Sutent (sunitinib capsules); AND
C) The patient has tried Stivarga® (regorafenib tablets); AND
D) Afinitor will be used in combination with imatinib (Gleevec tablets, generics), Sutent, or Stivarga.

10. Hodgkin Lymphoma, Classical (nodular sclerosis, mixed cellularity, lymphocyte depleted, and lymphocyte-rich subtypes of Hodgkin lymphoma). Approve for 3 years in adults ≥ 18 years of age with relapsed or refractory classical Hodgkin lymphoma.

11. Meningioma. Approve for 3 years if the patient has recurrent or progressive disease.

12. 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 (e.g., 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) The patient has not responded to primary therapy (e.g., 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; OR

B) The patient has progressive or relapsed disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Afinitor 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.

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. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on May 25, 2020. Search term: everolimus.

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.)

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

REFERENCES

289. Alecensa® capsules [prescribing information]. South San Francisco, CA: Genentech; June 2018.
290. 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.

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

36. 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.)

300. 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. Alunbrig™ tablets [prescribing information]. Cambridge, MA: ARIAD/Takeda Pharmaceuticals; May 2020.
292. 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.
293. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Ayvakit® (avapritinib tablets – Blueprint Medicines)

DATE REVIEWED: 01/15/2020

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. 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

According to the National Comprehensive Cancer Network (NCCN) soft tissue sarcoma guidelines (version 6.2019 – February 10, 2020), Ayvakit is one of the primary treatment options (category 2A) for GIST with *PDGFRA* exon 18 mutation, including *PDGFRA* D842V mutations.[2] 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. Upon disease progression on imatinib, Sutent® (sunitinib tablets) is a category 1 recommended option. The guidelines note that there are no appropriate treatment options for GIST progressing on Ayvakit. For disease progression on Sutent, Stivarga is the recommended option (category 1). Ayvakit is listed as one of the recommended therapies after disease progression on imatinib, Sutent, and Stivarga. Based on limited data, the guidelines recommend other small molecule inhibitors such as Nexavar® (sorafenib tablets), Votrient® (pazopanib tablets), Tasigna® (nilotinib tablets), and everolimus + TKI (all category 2A). Sprycel® (dasatinib tablets) is also recommended, based on limited data, for patients with *PDGFRA* D842V mutation (category 2A).

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

38. Gastrointestinal Stromal Tumor (GIST). Approve for 3 years if the patient meets the following criteria (A and B):
- **A)** The patient has unresectable or metastatic disease; 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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Ayvakit 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.

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 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 3, 2020.

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

134. 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.

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

518. Balversa™ tablets [prescribing information]. Horsham, PA: Janssen Pharmaceuticals; April 2019.
519. 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.
520. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Bosulif® (bosutinib tablets – Pfizer)

DATE REVIEWED: 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 3 years in duration.

AUTOMATION: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

37. 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

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

REFERENCES

294. Bosulif® tablets [prescribing information]. New York, NY: Pfizer Inc; October 2019.
295. Gleevec® tablets [prescribing information]. East Hanover, NJ: Novartis; July 2018.
296. Sprycel® tablets [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; December 2018.
297. Tasigna® capsules [prescribing information]. East Hanover, NJ: Novartis; September 2019.
298. Iclusig® tablets [prescribing information]. Cambridge, MA: Ariad Pharmaceuticals; January 2020.
299. 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.
300. 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.

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
301. Braftovi capsules [prescribing information]. Boulder, CO: Array BioPharma; April 2020.
302. 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.
303. 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.
304. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Brukinsa™ (zanubrutinib capsules – BeiGene)

DATE REVIEWED: 06/03/2020

OVERVIEW
Brukinsa, a kinase inhibitor, is indicated for the treatment of adults with mantle cell lymphoma who have received at least one prior therapy.[1] The indication was granted under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

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 regiments containing rituximab and cytarbine are used for patients depending on fitness. Many targeted therapies are now available. Stem cell transplants is also an option.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for B-cell lymphomas (version 1.2020 – January 22, 2020) provide recommendations for patients with mantle cell lymphoma.[2] Various agents and chemotherapy regimens are recommended, many of which are given intravenously (IV) and involve rituximab-based therapies. For second-line therapy for patients with short response duration to prior chemoimmunotherapy preferred regimens include Bruton's tyrosine kinase (BTK) inhibitors Calquence® (acalabrutinib capsules); Imbruvica® (ibrutinib capsules and tablets) with or without a rituximab product; Brukinsa; Revlimid® (lenalidomide capsules) with or without a rituximab product; and Venclexta® (venetoclax tablets) [all 2A recommendations]. For second-line therapy for extended response duration prior to chemoimmunotherapy, preferred regimens include BTK inhibitors (Calquence; Imbruvica with or without a rituximab product; and Brukinsa); Revlimid with or without a rituximab product; Treanda® (bendamustine injection for intravenous use) with or without a rituximab product (if not previously given); and Velcade® (bortezomib injection for intravenous or subcutaneous use) with or without rituximab (all 2A recommendations).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Brukinsa.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Brukinsa is recommended in those who meet the following criteria.

FDA-Approved Indication

1. **Mantle Cell Lymphoma.** Approve for 3 years if the patient has tried at least one prior therapy. Note: Example of therapies are Calquence® (acalbrutinib 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).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

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

REFERENCES

161. Brukinsa™ capsules [prescribing information]. San Mateo, CA: BeiGene; November 2019.
162. 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 June 4, 2020.
163. Maddocks K. Update on mantle cell lymphoma. *Blood*. 2018;132(16):1647-1656.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Cabometyx™ (cabozantinib tablets – Exelixis Inc.)

DATE REVIEWED: 02/05/2020

OVERVIEW

Cabometyx is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma (RCC).[1] It is also indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with Nexavar® (sorafenib tablets).

Guidelines

In the National Comprehensive Cancer Network (NCCN) clinical practice guidelines for kidney cancer (version 2.2020 – August 5, 2019), the recommendations for first-line oral therapy regimens in favorable risk patients with relapsed or Stage IV RCC with predominant clear cell histology are: Sutent® (sunitinib malate capsules), Votrient® (pazopanib tablets), Inlyta® (axitinib tablets) + Keytruda (pembrolizumab for injection) [all category 2A] are the preferred regimnes. 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 oral regimen is Cabometyx (category 2A). Inlyta is a category 2B agent that is useful under certain circumstances. 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 and everolimus are other recommended regimens (both category 2A).

The NCCN hepatobiliary cancers (version 4.2019 – December 20, 2019) recommends Nexavar and Lenvima as preferred first-line systemic therapy options.[3] Nexavar is a category 1 recommended option for Child-Pugh Class A or category 2A recommendation for Child-Pugh Class B7. Lenvima is a category 2A recommendation for Child-Pugh Class A only. The following are subsequent therapy options if there is disease progression: Stivarga (regorafenib tablets) [Child-Pugh Class A only; Category 1], Cabometyx (Child-Pugh Class A only; Category 1), Cyramza® (ramucirumab for intravenous injection) [Category 1], Opdivo (nivolumab for intravenous injection) [Child-Pugh Class A or B7; Category 2A], Nexavar (after first-line Lenvima; Category 2A), and Keytruda (pembrolizumab for intravenous injection) [Category 2A].

The NCCN Non-Small Cell Lung Cancer (NSCLC) guidelines (version 2.2020 – December 23, 2019) recommend cabozantinib for RET gene rearrangements (category 2A).[4] This is based on results from a small case series and a Phase II study in 25 patients.[5-6] Cabometyx 60 mg dose was used in the case series and the Phase II study. In the Phase II study, the rate of partial response was 28% and the median duration of response was 7.0 months.[6] At the time of data cutoff, 76% of the patients either had disease progression or died. The median progression-free survival (PFS) was 5.5 months and the median overall survival was 9.9 months.

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

38. Renal Cell Carcinoma (RCC), Advanced (Predominant Clear Cell or Non-Clear Cell Histology). Approve for 3 years.

2. Hepatocellular Carcinoma. Approve for 3 years if the patient has been previously treated with at least one tyrosine kinase inhibitor therapy (e.g., Nexavar® (sorafenib tablets), Lenvima [lenvatinib capsules]).

Other Uses with Supportive Evidence

3. Non-Small Cell Lung Cancer with RET Gene Rearrangements. Approve for 3 years.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Cabometyx 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 Cabometyx 60 mg tablets in men with mCRPC are published.[7] 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.[8]

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

164. Cabometyx™ [prescribing information]. San Francisco, CA: Exelixis Inc; January 2019.
165. 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 January 30, 2020.
166. The NCCN Hepatobiliary 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 January 30, 2020.
167. Chouieri TK, Halabi S, Sanford BL, et al. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: The alliance A031203 CABOSUN trial. *J Clin Oncol*. 2016;35:591-597.
168. 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 30, 2020.
169. Drilon A, Wang L, Hasanovic A, et al. Response to cabozantinib in patients with RET fusion-positive lung adenocarcinomas. *Cancer Discov*. 2013;3:630-635.
170. Drilon AE, Rekhtman N, Arcila M et al. Cabozantinib in patients with advanced RET-rearranged non-small cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. *Lancet Oncol*. 2016;17:1653-1660.
171. 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.
172. 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).

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Calquence® (acalabrutinib capsules – AstraZeneca)

DATE REVIEWED: 06/03/2020

OVERVIEW

Calquence is a Bruton tyrosine kinase (BTK) inhibitor indicated for the treatment of adults with mantle cell lymphoma who have received at least one prior therapy.[1] Calquence is also indicated for the treatment of adults with chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL).

Disease Overview

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 (LDH).

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 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

The National Comprehensive Cancer Network (NCCN) guidelines for B-cell lymphomas (version 1.2020 – January 22, 2020) provide recommendations for patients with mantle cell lymphoma.[3] Various agents and chemotherapy regimens are recommended, many of which are given intravenously (IV) and involve rituximab. Calquence is recommended as one of several preferred agents as second-line therapy in various clinical scenarios (category 2A).

The NCCN guidelines for CLL/SLL (version 4.2020 – December 20, 2019) 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.[4] In some clinical scenarios, Calquence is recommended to be given with Gazyva® (obinutuzumab injection for intravenous use).

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

39. Mantle Cell Lymphoma. Approve for 3 years.

40. Chronic Lymphocytic Leukemia (CLL). Approve for 3 years.

41. Small Lymphocytic Lymphoma (SLL). Approve for 3 years.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Calquence 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.)

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

256. Calquence® capsules [prescribing information]. Wilmington, DE: AstraZeneca; November 2019.
257. Wang M, Rule S, Zinzani PF, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicenter, phase 2 trial. *Lancet*. 2018;391(10121):659-667.
258. 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.
259. 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.

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.)

4. **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.

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

173. Caprelsa® [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; July 2016.
174. 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.
175. 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.
176. 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.

177. 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.
178. 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.
179. 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.

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

180. Cometriq™ [prescribing information]. San Francisco, CA: Exelixis Inc; January 2020.
181. 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.
182. 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.
183. 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.
184. 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.
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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Copiktra™ (duvelisib capsules – Verastem)

REVIEW DATE: 10/09/2019

OVERVIEW

Copiktra, an inhibitor of phosphatidylinositol 3-kinase delta and gamma, is indicated for the treatment of adults with 1) relapsed or refractory chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) after at least two prior therapies; and 2) relapsed or refractory follicular lymphoma after at least two prior systemic therapies.[1] Accelerated approval was given for the indication of follicular lymphoma based on overall response rate; continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Disease Overview

Chronic lymphocytic leukemia (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

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for CLL/SLL (version 1.2020 – August 23, 2019) address CLL. Copiktra is one of several therapies for relapsed or refractory therapy (category 2A).[3] 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 5.2019 – September 23, 2019) recommend Copiktra as second-line and subsequent therapy in patients with follicular lymphoma (grade 1-2) among patients relapsed or refractory after two prior therapies.[4]

The NCCN clinical practice guidelines for B-Cell Lymphomas (version 5.2019 – September 23, 2019) recommend Copiktra as second-line and subsequent therapy for marginal zone lymphomas that are refractory or refracotyr 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 3 years in duration unless otherwise 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

6. **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).

7. **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

Copiktra 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.)

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

186. Copiktra™ capsules [prescribing information]. Foster City, CA: Gilead Sciences; September 2018.
187. Hallek M, Shanafelt TD, Eichhorst B. Chronic lymphocytic leukemia. *Lancet*. 2018;391:1524-1537.
188. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma 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 October 4, 2019.
189. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 5.2019 – September 23, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 4, 2019.

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

305. Cotellic tablets [prescribing information]. South San Francisco, CA: Genentech USA Inc./Roche; January 2018.
306. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Daurismo™ (glasdegib tablets – Pfizer)

REVIEW DATE: 12/11/2019

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 adult patients who are ≥ 75 years of age or who have comorbidities that preclude use of intensive induction chemotherapy. Limitation of use. Daurismo has not been studied in patients with the comorbidities of severe renal impairment or moderate to severe hepatic impairment. The recommended dose is 100 mg orally once daily (QD) on Days 1 to 28 in combination with cytarabine 20 mg subcutaneously (SC) twice daily (BID) on Days 1 to 10 of each 28-day cycle. Dosage modifications of Daurismo are recommended in some clinical circumstances (e.g., QTc interval prolongation, hematologic toxicities, nonhematologic toxicity).

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. 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.

Clinical Efficacy

The efficacy of Daurismo in combination with low-dose cytarabine was assessed in a multicenter, open-label, randomized study called BRIGHT AML 1003.[1,3] The trial included 115 patients ≥ 55 years of age with newly-diagnosed AML who met at least one of the following criteria: 1) age ≥ 75 years, 2) severe cardiac disease, 3) baseline Eastern Cooperative Oncology Group (ECOG) performance status, or 4) baseline serum creatinine > 1.3 mg/dL. Patients were randomized (2:1) to receive Daurismo 100 mg QD with low-dose cytarabine 20 mg SC BID on Days 1 to 10 of a 28-day cycle (n = 77) or low-dose cytarabine alone (n = 38) in 28-day cycles until disease progression or unacceptable toxicity. Patients were stratified by cytogenetic risk (good/intermediate or poor). Efficacy was evaluated on the basis of overall survival from the date of randomization to death from any cause. With a median follow-up of approximately 20 months, Daurismo used with low-dose cytarbine (n = 77) was superior compared with the cytarbine alone arm (n = 38) as the median overall survival was 8.3 months and 4.3 months, respectively.[1] Other data are also available.[4-6]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for AML (version 2.2020 – September 2, 2019) are extensive. For patients ≥ 60 years of age who are not candidates for intensive remission induction therapy or declines intensive therapy, therapeutic options for patients without actionable mutations include 1) lower intensity therapy (azacitibine, decitabine [preferred]); 2) Venclexta™ (venetoclax tablets) with either intravenous (IV) decitabine, SC or IV azacitidine, or SC low-dose cytarabine; 3) Daurismo plus low-dose cytarabine; 4) low-dose cytarbine; 5) Mylotarg® (gemtuzumab ozogamicin injection for IV use) [CD33-positive]; or 6) best supportive care. Other recommendations are made in this clinical scenario based on the specific mutation. Daurismo can also be continued, along with low-dose cytarabine, as AML post-induction therapy for patients ≥ 60 years of age who had a response to previous low-intensity therapy.

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 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 Indications

135. Acute Myeloid Leukemia (AML). Approve for 3 years if the patient meets the following criteria (A and B):
- **A)** The patient is using Daurismo in combination with cytarabine; AND
- **B)** The patient must meet one of the following criteria (i or ii):
  - **i.** The patient is using Daurismo for treatment induction and meets one of the following (a or b)
    - **a)** The patient is ≥ 75 years of age; OR
    - **b)** According to the prescriber the patient has comorbidities that preclude the use of intensive induction chemotherapy; OR
  - **ii.** The patient is continuing Daurismo as post-induction therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Daurismo 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.)

131. 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

521. Daurismo™ tablets [prescribing information]. New York, NY: Pfizer; November 2018.
522. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (Version 2.2020 – September 2, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 4, 2020.
523. Cortes JE, Heidel FH, Hellmann A, et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. *Leukemia*. 2019;33(2):379-389.
524. Cortes JE, Smith BD, Wang ES, et al. Glasdegib in combination with cytarabine and daunorubicin in patients with AML or high-risk MDS: Phase 2 study results. *Am J Hematol*. 2018;93(11):1301-1310.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Erivedge® (vismodegib capsules – Genentech)

REVIEW DATE: 10/16/2019

OVERVIEW

Erivedge is indicated for the treatment of adults with metastatic basal cell carcinoma (BCC), or with locally advanced BCC that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.[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.

Disease Overview

Localized BCC is most commonly treated with surgery or radiation therapy (RT) and BCC is usually cured by local therapy.[2] Few options exist in the scenario of disease progression; however, hedgehog pathway inhibitors have provided a new option for patients with advanced disease and in those who are not amenable to local therapy. The sonic hedgehog signaling pathway has emerged as playing a pivotal role in the parthenogenesis of BCC. Mutations in the patched (PTCH) gene on chromosome 9q, which codes for the sonic hedgehog receptor, are the underlying cause of nevoid BCC syndrome and are frequently present in sporadic BCC.

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines for BCC (version 1.2019 – August 31, 2018) 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 or clinical trials should be considered.

For central nervous system cancers, NCCN guidelines (version 2.2019 – September 16, 2019) 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.

Safety

Erivedge has a Boxed Warning stating that it may cause fetal harm when administered to a pregnant woman.[1] Pregnancy status should be verified prior to initiation of therapy. Female patients should use contraception during and for 24 months after the final dose. Male patients should use contraception to avoid exposure to a partner of childbearing potential during and for 3 months after the final dose.

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 (BCC), Metastatic. Approve for 3 years.

50. Basal Cell Carcinoma (BCC), Locally Advanced. Approve for 3 years if the patients meets ONE of the following conditions (A or B):

~~77.~~ Initial Therapy. Approve if the patient meets ONE of the following (i or ii):

i. The patient's basal cell carcinoma has recurred following surgery or radiation therapy; OR

ii. The patient meets BOTH of the following (a and b):

a) The patient is not a candidate for surgery; AND

~~a.~~ According to the prescribing physician, the patient is not a candidate for radiation therapy.

78. Patients 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) The patient has tried at least one chemotherapy agent.
Note: Examples of chemotherapy include etoposide, carboplatin, cisplatin; AND

B) According to the prescriber, the patient has a mutation of the sonic hedgehog pathway.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Erivedge 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.)

8. 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 BCC, 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 BCC who had progressed on Erivedge that showed resistance to Odomzo, another hedgehog signaling pathway used in BCC.[7] This criterion was developed based on the professional opinion of specialized physicians.

9. Metastatic Colorectal Cancer (mCRC). Erivedge is not recognized in the treatment recommendations for colon cancer from the NCCN (version 2.2019 – May 15, 2019).[4] In combination with standard of care treatment for first-line mCRC, 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 mCRC.[3] Adults with histologically confirmed mCRC and Eastern Cooperative Oncology Group (ECOG) performance score (PS) of 0 or 1 were randomized 1:1 to Erivedge or placebo (n = 199). Median PFS was 9.3 months vs. 10.1 months, respectively (hazard ratio [HR] 1.25; 95% confidence interval [CI]: 0.89, 1.76; P = 0.28). At data cutoff, 45 patients had died, yielding a 12-month Kaplan Meier overall survival (OS) rate of 81.4% and 80.1% for Erivedge and placebo, respectively.

10. Ovarian Cancer. The NCCN guidelines for Ovarian Cancer (version 2.2019 – September 17, 2019) 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 (CR) after their most recent chemotherapy regimen; all patients had baseline ECOG PS of 1 or less (n = 104). PFS from time of randomization for patients treated with Erivedge was 7.5 months compared with 5.8 months for placebo (HR 0.79; 95% CI: 0.46, 1.35; P = 0.39). When assessed by remission status, a similar non-statistically significant improvement in PFS was noted among patients in second CR (n = 84); the median PFS in patients treated with Erivedge was 7.5 months vs. 5.6 months for placebo (HR 0.44; 95% CI: 0.36, 1.20; P = 0.17). For patients in third CR (n = 20), median PFS was shorter with Erivedge (5.6 months) than placebo (7.5 months) [HR 1.79; 95% CI: 0.50, 6.48; P = 0.37).

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

190. Erivedge® capsules [prescribing information]. South San Francisco, CA: Genentech USA, Inc.; February 2019.
191. The NCCN Basal Cell Skin Cancer Clinical Practice Guidelines in Oncology (Version 1.2019 – August 31, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 23, 2019.
192. 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.
193. NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 2.2019 – May 15, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 23, 2019.
194. 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.
195. NCCN Ovarian Cancer Clinical Practice Guidelines in Oncology (Version 2.2019 – September 17, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 23, 2019.
196. 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.
197. NCCN Central Nervous System 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 September 23, 2019.

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.)

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

260. Erleada™ [prescribing information]. Horsham, PA: Janssen Pharmaceutical Companies; September 2019.
261. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Erlotinib (Tarceva® tablets – Genentech/Astellas/OSI Pharmaceuticals; generics)

DATE REVIEWED: 03/11/2020

OVERVIEW

Erlotinib, a kinase inhibitor, is indicated for the 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 receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen.[1] Erlotinib continues to be indicated for the first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer, in combination with gemcitabine. In patients with NSCLC, erlotinib is not recommended for use in combination with platinum-based chemotherapy. The safety and efficacy of erlotinib have not been established in patients with NSCLC whose tumors have other EGFR mutations.

Guidelines

FDA-Approved Indications

The National Comprehensive Cancer Network (NCCN) guidelines for NSCLC (version 3.2020 – February 11, 2020) 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) is a category 2A recommended option. Upon disease progression, T790M testing is recommended in guidelines. Tagrisso is a category 1 recommended option if T790M mutation-positive. Patients with symptomatic progression to the brain can consider local therapy, Tagrisso (if T790M mutation-positive) [category 1], or continue on erlotinib (± Cyramza or bevacizumab), Iressa, or Gilotrif (category 2A). Tagrisso (regardless of T790M status) or pulse erlotinib can be considered for progressive leptomeningeal disease.

The NCCN guidelines for central nervous system cancers (version 3.2019 – October 18, 2019) recommend erlotinib as weekly pulse therapy for leptomeningeal metastases from NSCLC with an *EGFR* exon 19 deletion or exon 21 (L858R) mutation in patients with positive cerebrospinal fluid (CSF) cytology and progression after receiving intra-CSF chemotherapy (category 2B).[3] Erlotinib, Gilotrif, and Iressa are

recommended for brain metastases due to NSCLC; Tagrisso is recommended for T790M mutation-positive NSCLC (all category 2A).

NCCN guidelines for pancreatic adenocarcinoma (version 1.2020 – November 26, 2019) 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). The guidelines state that although this combination significantly improved survival, the actual benefit was small, suggesting that only a subset of patients benefit. Erlotinib and gemcitabine is also recommended for second-line therapy for recurrent disease if prior fluoropyrimidine-based therapy is given (category 2A).

Other Uses with Supportive Evidence

The NCCN guidelines for Kidney Cancer (version 2.2020 – August 5, 2019) 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] The NCCN panel lists clinical trial and Sutent® (sunitinib capsules) as the preferred options for this indication. Erlotinib, either as monotherapy or in combination with bevacizumab (combination therapy for selected patients with advanced papillary RCC), are category 2A recommended options.

The NCCN bone cancer guidelines (version 1.2020 – August 12, 2019) 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).

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) – Epidermal Growth Factor Receptor (EGFR) Mutation-Positive. Approve for 3 years if the patient meets the following criteria (A and B):
- ~~**79.**~~ The patient has *metastatic* NSCLC; AND
- ~~**80.**~~ The patient meets ONE of the following criteria (i or ii):
  - **i.** The patient has epidermal growth factor receptor (EGFR) exon 19 deletions as detected by an approved test; OR
  - **ii.** The patient has exon 21 (L858R) substitution mutations as detected by an approved test.

53. Pancreatic Cancer, Locally Advanced, Unresectable, or Metastatic. Approve for 3 years if prescribed in combination with gemcitabine.

Other Uses with Supportive Evidence

3. Renal Cell Carcinoma (RCC), Advanced – Non-Clear Cell Histology. Approve for 3 years.

4. Bone Cancer – Chordoma. Approve for 3 years in patients who have tried at least one previous therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Erlotinib 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. **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 patients with 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).

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.

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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):
- **81.** Farydak will be taken in combination with Velcade® (bortezomib injection) and dexamethasone; AND
- **82.** 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.)

14. 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]

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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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Gavreto Prior Authorization Policy
- Gavreto™ (pralsetinib capsules – Blueprint Medicines Corporation)

REVIEW DATE: 09/09/2020

OVERVIEW

Gavreto, a kinase inhibitor, is indicated for the treatment of 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.[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 trial(s).

Guidelines

The National Comprehensive Cancer Network (NCCN) has not addressed the use of Gavreto for the treatment of NSCLC.

POLICY STATEMENT

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

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

136. Non-Small Cell Lung Cancer. 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 metastatic disease; AND
- **C)** Patient has rearranged during transfection (RET) fusion-positive disease detected by an Food and Drug Administration (FDA) approved test; AND
- **D)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Gavreto is not recommended in the following situations:

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

REFERENCES

525. Gavreto capsules [prescribing information]. Cambridge, MA: Blueprint Medicines Corporation; September, 2020.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Gilotrif™ (afatinib tablets – Boehringer Ingelheim)

DATE REVIEWED: 12/04/2019

OVERVIEW

Gilotrif 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 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. Gilotrif is also indicated for the treatment of patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for NSCLC (version 1.2020 – November 6, 2019) 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. Tagrisso is a category 1 recommended option if the NSCLC is T790M mutation-positive. 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 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):
   ~~**83.**~~ The patient has *metastatic* NSCLC; AND
   ~~**84.**~~ The 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) The patient has metastatic squamous cell carcinoma; AND
   B) The patient has disease progression after treatment with platinum-based chemotherapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Gilotrif 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.)

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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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Ibrance® (palbociclib capsules and tablets – Pfizer Labs)

DATE REVIEWED: 04/15/2020

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[1-3]; or
2. Fulvestrant in patients with disease progression following endocrine therapy.[1,4-5]

Disease Overview
Based on molecular profiling, breast cancer is classified as HR+ (estrogen receptor positive [ER+] and/or progesterone receptor positive [PgR+]), HER2+, or triple negative (ER-negative, PgR-negative, and HER2-negative).[6-7] Most breast cancers in women (71%) are HR+, HER2-negative; these cancers tend to be slow-

growing and less aggressive than other subtypes.[7] HR+, HER2-negative tumors are associated with the most favorable prognosis compared with other subtypes, particularly in the short-term, in part because expression of hormone receptors is predictive of a favorable response to hormonal therapy. In men, about 85% of breast cancers are ER+ and 70% are PgR+.[8] About 12% of breast cancers are HR+ and HER2+, and tend to be higher grade and more aggressive than HR+ cancers.[7] About 5% of breast cancers are HER2+ and do not express hormone receptors. These cancers tend to be more aggressive than other breast cancers and have a poorer short-term prognosis compared with ER+ breast cancers. About 12% of breast cancers in women are triple negative and have a poorer short-term prognosis than other subtypes.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on breast cancer (version 3.2020 – March 6, 2020) recommend any of the CDK4/6 inhibitors in combination with an AI or fulvestrant as a first-line 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).[9,12] The compendium recommend 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.[10] The NCCN guidelines state in a footnote that if there is disease progression on CDK4/6 inhibitor therapy, there are limited data to support an additional line of therapy with another CDK4/6-containing regimen.[9] The limited data are based on a multicenter analysis which evaluated clinical outcomes in patients (n = 58) with HR+/HER2-negative metastatic breast cancer who received Verzenio after disease progression on Ibrance or Kisqali.[13] 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. There are no published data with additional line of therapy with Ibrance or Kisqali, if the patient has progressed on Verzenio.

In men with breast cancer, tamoxifen is generally used rather than an AI, because the data supporting use of an AI in men are limited.[8-9] The use of AI therapy with LHRH has been reported. Only limited data are available with Kisqali use in men with breast cancer as first-line endocrine therapy in combination with anastrozole, exemestane, or letrozole or for combination use with fulvestrant. However, available real-world data suggest comparable efficacy and safety profiles in men as in women; it is reasonable to recommend CDK4/6 inhibitors in combination with an aromatase inhibitor or fulvestrant, everolimus, and PIK3CA inhibitors to men based on extrapolation of data from studies comprised largely of female participants with advanced breast cancer.

The NCCN guidelines on soft tissue sarcoma (version 6.2019 – February 10, 2020) recommend Ibrance as single-agent therapy for the treatment of WD-DDLS for retroperitoneal sarcomas (category 2A).[11]

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, C, and D):
- **85.** Patient has advanced or metastatic hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND
- **86.** Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
- **87.** The 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; AND
- **D)** The patient has not had disease progression while on Ibrance, Kisqali (ribociclib tablets), or Verzenio (abemaciclib tablets).

***** 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, D, and E):
- **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)** The patient is receiving ovarian suppression/ablation with a gonadotropin-releasing hormone (GnRH) agonist (e.g., Lupron [leuprolide], Trelstar [triptorelin], Zoladex (goserelin]), or has had surgical bilateral oophorectomy or ovarian irradiation; AND
- **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; AND
- **E)** Patient has not had disease progression while on Ibrance, Kisqali (ribociclib tablets), or Verzenio (abemaciclib tablets).

***** Refer to the Policy Statement.

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) agonist (e.g., Lupron [leuprolide], Trelstar [triptorelin], Zoladex (goserelin]); AND
    - **b)** Ibrance will be used in combination with anastrozole, exemestane, or letrozole; OR
  - **ii.** Ibrance will be used in combination with fulvestrant; AND
- **D)** Patient has not had disease progression while on Ibrance, Kisqali (ribociclib tablets), or Verzenio (abemaciclib tablets).

***** 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

Ibrance 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.

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	Breast Cancer in Women: • The word "initial" was added to first-line endocrine therapy.	03/07/2018

	• LHRH agonist was replaced with GnRH agonist. • Prior endocrine therapy that was previously a list of examples, was revised to be a list of at least one of the listed endocrine therapies. Afinitor plus Faslodex or tamoxifen and exemestane plus Afinitor were added to the list and "high-dose" was removed from ethinyl estradiol. Ibrance, Kisqali and Verzenio are endocrine therapies not included in this list. • Added a criterion that applies to all of the indications in women that the patient has not had disease progression while on Ibrance, Kisqali, or Verzenio. Breast Cancer in Men: • LHRH agonist was replaced with GnRH agonist. • The word "initial" was added to first-line endocrine therapy. Tamoxifen was added to the list of first-line (initial) endocrine therapies. • Added a criterion that the patient has not had disease progression while on Ibrance, Kisqali, or Verzenio.	
Selected revision	Separated out criteria for Postmenopausal and Pre/Perimenopausal women for clarity. Under Breast Cancer in Men criteria, deleted tamoxifen from list of endocrine therapy agents that can be used as combination therapy with Ibrance. Added Ibrance plus Faslodex combination therapy as option for men if progressed on at least one endocrine therapy.	09/12/2018
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. NCCN 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

LHRH – Luteinizing hormone-releasing hormone; GnRH – gonadotropin-releasing hormone;

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Iclusig (ponatinib tablets – ARIAD/Takeda)

DATE REVIEWED: 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 3 years in duration.

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

Iclusig 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.)

18. 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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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Idhifa® (enasidenib tablets – Celgene/Agios)

DATE REVIEWED: 02/05/2020

OVERVIEW

Idhifa, an isocitrate dehydrogenase-2 (IDH2) inhibitor, is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an IDH2 mutation as detected by an FDA-approved test.[1] The recommended dose is 100 mg orally once daily (QD) until disease progression or unacceptable toxicity. Inhibition of the mutant IDH2 enzyme by Idhifa led to decreased 2-hydroxyglutarate (2-HG) levels and induced myeloid differentiation.

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 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 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.

Clinical Efficacy

The efficacy of Idhifa was assessed in an open-label, single-arm, multicenter, two-cohort clinical study involving 199 adult patients with relapsed or refractory AML that had an IDH2 mutation.[1] Patients were assigned to receive Idhifa 100 mg QD. The median patient age was 68 years and patients had received a median of two prior therapies. Approximately 79% of patients were transfusion dependent at baseline. Of the IDH2 mutations, 78% of patients had R140 and 22% of patients had R172. The median follow-up was 6.6 months. In total, 19% of patient attained complete remission (defined as < 5% blasts in the bone marrow, no evidence of disease and full recovery of peripheral blood counts [platelets > 100,000/microliter and absolute neutrophil counts > 1,000/microliter]). Approximately 4% of patients obtained complete remission with partial hematological recovery (defined as < 5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts [platelets > 50,000/microliter and absolute neutrophil count > 500/microliter]). For patients who obtained complete remission or complete remission with partial hematologic recovery, the median time to first response was 1.9 months (range, 0.5 to 7.5 months); the median time to best response among these patients was 3.7 months (range, 0.6 to 11.2 months). For the 157 patients who were dependent upon red blood cell (RBC) and/or platelet transfusions at baseline, 34% of patients (n = 53/157) became independent of RBC and platelet transfusions.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on AML (version 3.2020 – December 23, 2019) 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] Other more common adverse events (AEs) include nausea (50%), diarrhea (43%), vomiting (34%), and decreased appetite (34%). Elevated bilirubin levels were reported in 81% of patients, of which 15% were Grade ≥ 3 in severity.

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

Idhifa 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.)

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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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Imatinib (Gleevec) [imatinib mesylate tablets for oral use – Novartis, generic]

DATE REVIEWED: 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.

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

Imatinib 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.)

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

214. Gleevec® tablets [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals, Inc.; July 2018.
215. Imatinib tablets [prescribing information]. Cranbury, NJ and Jacksonville, FL: Sun Pharmaceuticals and Ranbaxy Pharmaceuticals; October 2016.
216. Tasigna® capsules [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals, Inc.; September 2019.
217. Sprycel® tablets [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; December 2018.
218. Bosulif® tablets [prescribing information]. New York, NY: Pfizer Inc; October 2019.
219. Iclusig® tablets [prescribing information]. Cambridge, MA: Takeda/Ariad Pharmaceuticals; January 2020.
220. 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.
221. 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.
222. 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.
223. 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.
224. 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.
225. 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.
226. 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.
227. 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.
228. 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.

229. 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.
230. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Imbruvica® (ibrutinib tablets and capsules – Pharmacyclics/Janssen)

DATE REVIEWED: 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 3 years in duration unless otherwise 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

21. **Central Nervous System (CNS) Lymphoma (Primary).** Approve for 3 years if according to the prescribing physician the patient has relapsed or refractory disease.

22. **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.

23. **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

Imbruvica 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.)

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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232. 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.
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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.

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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241. 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.
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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:

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

REFERENCES

321. Inqovi® tablets [prescribing information]. Princeton, NJ and Japan: Taiho Oncology, Inc. and Otsuka Pharmaceutical Co.; July 2020.
322. Dacogen® injection for intravenous use [prescribing information]. Rockville, MD and Dublin, CA: Otsuka American Pharmaceutical and Astex Pharmaceuticals; June 2020.
323. 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.

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 $\geq 10 \times 10^9$/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:

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

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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:

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
324. Iressa® tablets [prescribing information]. Wilmington, DE: AstraZeneca; July 2018.
325. 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 August 31, 2020.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Jakafi® (ruxolitinib tablets – Incyte)

DATE REVIEWED: 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.)

26. 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.

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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252. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Kisqali® (ribociclib tablets – Pfizer Labs); Kisqali® Femara® Co-Pack (ribociclib tablets; letrozole tablets, co-packaged for oral use – Pfizer Labs)

DATE REVIEWED: 04/15/2020

OVERVIEW

Kisqali, a cyclin-dependent kinase (CDK) 4/6 inhibitor, is indicated in combination with an aromatase inhibitor (AI) as initial endocrine-based therapy for the treatment of pre/perimenopausal or postmenopausal women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.[1-3] Kisqali Femara Co-Pack has the same indication with the AI, letrozole being provided.[4] Kisqali (not Co-Pack) is also indicated in combination with fulvestrant for the treatment of postmenopausal women with HR+, HER2-negative advanced or metastatic breast cancer, as initial endocrine based therapy or following disease progression on endocrine therapy.

Disease Overview

Based on molecular profiling, breast cancer is classified as HR+ (estrogen receptor positive [ER+] and/or progesterone receptor positive [PgR+]), HER2+, or triple negative (ER-negative, PgR-negative, and HER2-negative).[5-6] Most breast cancers in women (71%) are HR+, HER2-negative; these cancers tend to be slow-growing and less aggressive than other subtypes.[6] HR+, HER2-negative tumors are associated with the most favorable prognosis compared with other subtypes, particularly in the short-term, in part because expression of hormone receptors is predictive of a favorable response to hormonal therapy. In men, about 85% of breast cancers are ER+ and 70% are PgR+.[7] About 12% of breast cancers are HR+ and HER2+, and tend to be higher grade and more aggressive than HR+ cancers.[6] About 5% of breast cancers are HER2+ and do not express hormone receptors. These cancers tend to be more aggressive than other breast cancers and have a poorer short-term prognosis compared with ER+ breast cancers. About 12% of breast cancers in women are triple negative and have a poorer short-term prognosis than other subtypes.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on breast cancer (version 3.2020 – March 6, 2020) recommend any of the CDK4/6 inhibitors in combination with an AI or fulvestrant as a first-line 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).[8] The compendium recommend 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.[9] The NCCN guidelines state in a footnote that if there is disease progression on CDK4/6 inhibitor therapy, there are limited data to support an additional line of therapy with another CDK4/6-containing regimen.[8] The limited data are based on a multicenter analysis which evaluated clinical outcomes in patients (n = 58) with HR+/HER2-negative metastatic breast cancer who received Verzenio after disease progression on Ibrance or Kisqali.[10] 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. There are no published data with additional line of therapy with Ibrance or Kisqali, if the patient has progressed on Verzenio.

In men with breast cancer, tamoxifen is generally used rather than an AI, because the data supporting use of an AI in men are limited.[7] The use of AI therapy with LHRH has been reported.[8-9] Only limited data are available with Kisqali use in men with breast cancer as first-line endocrine therapy in combination with anastrozole, exemestane, or letrozole or for combination use with fulvestrant. However, available real-world data suggest comparable efficacy and safety profiles in men as in women; it is reasonable to recommend CDK4/6 inhibitors in combination with an aromatase inhibitor or fulvestrant, everolimus, and PIK3CA inhibitors to men based on extrapolation of data from studies comprised largely of female participants with advanced breast cancer.

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

73. Breast Cancer in Postmenopausal Women*. Approve for 3 years if the patient meets the following criteria (A, B, C, and D):

88. Patient has advanced or metastatic hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND

89. Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND

90. The 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 ; AND

D) The patient has not had disease progression while on Kisqali, Ibrance (palbociclib capsules), or Verzenio (abemaciclib tablets).

***** 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 meets one of the following criteria (i or ii):

i. The patient meets both of the following criteria (a and b):

a) Kisqali will be used in combination with anastrozole, exemestane, or letrozole; AND

b) Patient is receiving ovarian suppression/ablation with a gonadotropin-releasing hormone (GnRH) agonist (e.g., Lupron [leuprolide], Trelstar [triptorelin], Zoladex (goserelin]), or has had surgical bilateral oophorectomy or ovarian irradiation; OR

ii. Kisqali will be used in combination with fulvestrant; AND

D) Patient has not had disease progression while on Kisqali, Ibrance (palbociclib capsules), or Verzenio (abemaciclib tablets).

***** 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, C, and D):

E) Patient has advanced or metastatic hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND

F) Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND

G) 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) agonist (e.g., Lupron [leuprolide], Trelstar [triptorelin], Zoladex (goserelin]); AND

b) Kisqali will be used in combination with anastrozole, exemestane, or letrozole; OR

ii. Kisqali will be used in combination with fulvestrant ; AND

H) Patient has not had disease progression while on Kisqali, Ibrance (palbociclib capsules), or Verzenio (abemaciclib tablets).

***** 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, C, and D):

74. Patient has advanced or metastatic hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND

75. Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND

76. If the patient is premenopausal or perimenopausal, then the patient is receiving ovarian suppression/ablation with a gonadotropin-releasing hormone (GnRH) agonist (e.g., Lupron [leuprolide], Trelstar [triptorelin], Zoladex (goserelin]), or has had surgical bilateral oophorectomy or ovarian irradiation; AND

D) The patient has not had disease progression while on Kisqali, Ibrance (palbociclib capsules), or Verzenio (abemaciclib tablets).

***** 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, 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)** The patient is receiving a gonadotropin-releasing hormone (GnRH) agonist (e.g., Lupron [leuprolide], Trelstar [triptorelin], Zoladex (goserelin]); AND
   - **D)** The patient has not had disease progression while on Kisqali, Ibrance (palbociclib capsules), or Verzenio (abemaciclib tablets).

   ***** Refer to the Policy Statement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Kisqali or Kisqali Femara 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.)

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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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.

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

REFERENCES

530. Koselugo™ capsules [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals; April 2020.

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.)

29. 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. Lenvima™ capsules [prescribing information]. Woodcliff Lake, NJ: Eisai Inc.; February 2020.
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.

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

77. 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.

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
336. Lonsurf® tablets [prescribing information]. Princeton, NJ: Taiho Oncology Inc.; February 2019.
337. 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.
338. 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.
339. 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.
340. 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.
341. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Lorbrena® (lorlatinib tablets – Pfizer)

DATE REVIEWED: 11/13/2019

OVERVIEW
Lorbrena, a kinase inhibitor, is indicated for the treatment of patients with anaplastic lymphoma kinase (*ALK*)-positive metastatic non-small cell lung cancer (NSCLC), whose disease has progressed on: Xalkori® (crizotinib capsules) and at least one other ALK inhibitor for metastatic disease; or Alecensa® (alectinib capsules) as the first ALK inhibitor therapy for metastatic disease; or Zykadia® (ceritinib capsules) as the first ALK inhibitor therapy for metastatic disease. 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.

GUIDELINES
According to the National Comprehensive Cancer Network (NCCN) NSCLC guidelines (version 1.2020 – November 6, 2019), Alecensa is noted as a category 1 preferred regimen.[2] Other category 1 recommended regimens are Alunbrig™ (brigatinib tablets) and Zykadia. Xalkori is listed as useful in certain circumstances, but it's also a category 1 option. Lorbrena is 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 (preferred) or Zykadia [both category 2A] for ROS1 rearrangement-positive NSCLC. Zykadia is noted 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) The patient has anaplastic lymphoma kinase (*ALK*)-positive metastatic NSCLC; AND
   B) The patient meets one of the following criteria (i, ii, or iii):
      i. The patient has disease progression on Xalkori (crizotinib capsules) and at least one other ALK inhibitor (e.g., Zykadia [ceritinib capsules], Alecensa [alectinib capsules], Alunbrig [brigatinib tablets]); OR
      ii. The patient has disease progression on Alecensa (alectinib capsules) as the first ALK inhibitor therapy; OR
      iii. The patient has disease progression on Zykadia (ceritinib capsules) as the first ALK inhibitor therapy.

Other uses With Supportive Evidence

2. **Non-Small Cell Lung Cancer – ROS1 Rearrangement-Positive.** Approve for 3 years if the patient has disease progression on Xalkori (crizotinib capsules) or Zykadia (ceritinib capsules).

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Lorbrena 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.

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
253. Lorbrena® tablets [prescribing information]. New York, NY: Pfizer Inc.; November 2018.
254. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 1.2020 – November 6, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on November 8, 2019.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Lynparza™ (olaparib capsules and tablets – AstraZeneca)

DATE REVIEWED: 01/15/2020; 05/27/2020 selected revision

OVERVIEW
Lynparza, a poly (ADP-ribose) polymerase (PARP) inhibitor, is indicated for the following[1]:
1) In adult patients with deleterious or suspected deleterious germline BReast CAncer (g*BRCA*)-mutated advanced **ovarian cancer** who have been **treated** with three or more prior lines of chemotherapy.

2) 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.
3) 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.
4) Indicated in combination with bevacizumab for the maintenance treatment of 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)** a deleterious or suspected deleterious BRCA mutation, and/or **b)** genomic instability.
5) In patients with deleterious or suspected deleterious g*BRCA* mutated, HER2-negative metastatic **breast cancer**, 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.
6) Maintenance treatment of adult patients with deleterious or suspected deleterious gBRCA mutated metastatic **pancreatic adenocarcinoma** whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.
7) For the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (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

The National Comprehensive Cancer Network (NCCN) guidelines on ovarian cancer (version 3.2019 – November 26, 2019) 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 for germline mutations; category 2A for somatic mutations). 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. note that the therapy options for patients with recurrent disease are primarily dependent on whether the patient is considered *platinum-resistant* (patients who relapse < 6 months after initial platinum chemotherapy) or *platinum-sensitive* (patients who relapse ≥ 6 months after initial platinum chemotherapy). 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).

The NCCN breast cancer guidelines (version 3.2019 – September 6, 2019) recommend Lynparza as one of the preferred single agents for HER2-negative, *BRCA* 1/2 positive tumors, in the recurrent or metastatic setting (category 1).[3]

The NCCN pancreatic adenocarcinoma guidelines (version 1.2020 – November 26, 2019) 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.

The NCCN prostate cancer guidelines (version 2.2020 – May 21, 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

78. Ovarian Cancer – Treatment.

A) Initial Therapy. Approve for 3 years if the patient meets the following criteria (i and ii):
- **i.** The patient has a germline *BRCA*-mutation as confirmed by an approved test; AND
- **ii.** The 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.

79. Ovarian, Fallopian Tube, or Primary Peritoneal Cancer – Maintenance, Monotherapy. Approve for 3 years if the patient meets one of the following criteria (A or B):

A) The patient meets both of the following criteria for first-line maintenance therapy (i and ii):
- **i.** The patient has a germline or somatic *BRCA* mutation-positive disease as confirmed by an approved test; AND
- **ii.** The patient is in complete or partial response to first-line platinum-based chemotherapy regimen (e.g., carboplatin with paclitaxel, carboplatin with doxorubicin, docetaxel with carboplatin); OR

B) The 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.

3. 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, and C):

A) The medication is used in combination with bevacizumab; AND

B) The 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

C) The 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.

4. Breast Cancer. Approve for 3 years if the patient meets the following criteria (A, B, C, and D):
A) The patient has metastatic, germline *BRCA* mutation-positive breast cancer; AND
B) The patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; 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 hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND
b) The patient meets ONE of the following criteria (1 or 2):
(1) The patient has been treated with prior endocrine therapy; OR
(2) The 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) The patient has been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting.

5. Pancreatic Cancer – Maintenance Therapy. Approve for 3 years if the patient meets the following criteria (A and B):
A) The patient has a germline *BRCA* mutation-positive metastatic disease; AND
B) 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, and E):
A) The patient has metastatic disease; AND
B) The 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. The patient has had a bilateral orchiectomy; AND
C) The 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*.
D) The patient does not have a *PPP2R2A* mutation; AND
E) The patient has been previously treated with abiraterone or Xtandi (enzalutamide capsules).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Lynparza 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.

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

REFERENCES
342. Lynparza™ capsules [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; May 2020.
343. The NCCN Ovarian Cancer Clinical Practice Guidelines in Oncology (Version 3.2019 – November 26, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on. January 13, 2020.
344. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 3.2019 – September 6, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 13, 2020.
345. The NCCN Pancreatic Adenocarcinoma Clinical Practice Guidelines in Oncology (Version 1.2020 – November 26, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 13, 2020.
346. 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 May 23, 2020.

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
347. Mekinist® tablets [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; June 2020.
348. 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.
349. 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.
350. 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.
351. 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.
352. 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.

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
353. Mektovi® tablets [prescribing information]. Boulder, CO: Array BioPharma; January 2019.
354. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Nerlynx™ (neratinib tablets – Puma Biotechnology)

DATE REVIEWED: 09/25/2019; selected revision 03/04/2020

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, randomized, double-blind, placebo-controlled, multicenter, pivotal study (ExteNET, Extended Adjuvant Treatment of Breast Cancer with Neratinib) in women with early stage HER2+ breast cancer (n = 2,840).[1,2] Patients had completed adjuvant treatment

with Herceptin and were without evidence of recurrence. Placebo or Nerlynx was given continuously for 12 months. The ExteNET trial underwent multiple amendments, and was a time driven analysis rather than event driven. Invasive disease-free survival (iDFS) within 2 years and 28 days was 94.2% (95% confidence interval [CI]: 92.6%, 95.4%) on Nerlynx vs. 91.9% (95% CI: 90.2%, 93.2%) on placebo (stratified hazard ratio [HR] 0.66; 95% CI: 0.49, 0.90; P =0.008). In a prespecified exploratory subgroup analysis of iDFS, Nerlynx was more beneficial in patients with HR+ 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% CI: 0.60, 1.43). In another analysis after a median follow-up of 5.2 years (interquartile range 2.1-5.3), patients who received Nerlynx had significantly fewer iDFS events than those in the placebo group (116 vs. 163 events; stratified HR 0·73; 95% CI: 0.57, 0.92; P = 0.0083).[3] The 5-year iDFS survival was 90·2% (95% CI: 88.3%, 91.8%) in the Nerlynx group and 87·7% ((95% CI: 85.7%, 89.4%) 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 2.2020 – February 5, 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+. For the treatment of recurrent or metastatic disease, Nerlynx + capecitabine is listed as a category 2B recommended option.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Nerlynx. Coverage with Nerlynx is recommended for 1 year (total) of a patient's lifetime.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

80. 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)** The patient meets ONE of the following criteria (i or ii):

ii. The medication is requested for extended adjuvant therapy after the patient has completed 1 year of adjuvant therapy with trastuzumab intravenous products; OR

iii. The 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) The 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) The 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

Nerlynx 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.)

33. **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]

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

355. Nerlynx™ tablets [prescribing information]. Los Angeles, CA: Puma Biotechnology, Inc.; February 2020.
356. 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.
357. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 2.2020 – February 5, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 2, 2020.
358. 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.

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

81. 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).

82. Differentiated (i.e. papillary, follicular, and Hürthle cell) Thyroid Carcinoma. Approve for 3 years if refractory to radioactive iodine therapy.

83. Hepatocellular Carcinoma (HCC), Unresectable. Approve for 3 years.

Other Uses with Supportive Evidence

~~84.~~ **Acute Myeloid Leukemia (AML).** Approve for 3 years if disease is *FLT3*-ITD mutation-positive as detected by an approved test.

85. Angiosarcoma. Approve for 3 years.

86. Chordoma. Approve for 3 years in patients with recurrent disease.

87. Desmoid Tumors (aggressive fibromatosis). Approve for 3 years.

88. Gastrointestinal Stromal Tumor (GIST). Approve for 3 years if the patient meets the following criteria (A, B, and C):
- **A)** Patient has previously tried imatinib (Gleevec® tablets, generics); AND
- **B)** Patient has previously tried Sutent (sunitinib capsules); AND
- **C)** Patient has previously tried Stivarga® (regorafenib tablets).

89. Medullary Thyroid Carcinoma. Approve for 3 years if the patient has tried Caprelsa® (vandetanib tablets) or Cometriq® (cabozantinib capsules).

90. 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.

91. 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.

92. 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.)

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

255. Nexavar® tablets [prescribing information]. Wayne, NJ: Bayer; December 2017.
256. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Nilutamide (Nilandron tablets – Concordia Pharmaceuticals Inc., generic)

DATE REVIEWED: 12/18/2019

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 4.2019 – August 19, 2019) 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

Nilutamide 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

265. Nilandron® [prescribing information]. St. Micheal, Barbados: Concordia Pharmaceutical Inc.; May 2017.
266. 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 December 10, 2019.

267. The NCCN Drugs & Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 10, 2019. Search term: nilutamide.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Ninlaro® (ixazomib capsules – Takeda)

DATE REVIEWED: 02/26/2020

OVERVIEW

Ninlaro is an oral proteasome inhibitor (PI) 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 is not established in patients < 18 years of age.

Disease Overview

Multiple myeloma is a cancer formed by malignant plasma cells.[5] 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, 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. If symptoms are suggestive of multiple myeloma, a diagnosis is made based on blood and urine testing, bone x-rays, and a bone marrow biopsy. Ninlaro is a reversible inhibitor of the chymotrypsin-like activity of the 20S proteasome.[1] Cancer cells have higher levels of proteasome activity vs. normal cells, making cancer cells more sensitive to the effects of Ninlaro.[2]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines, which address diagnosis, treatment, and follow-up for patients with multiple myeloma (version 2.2020 – October 9, 2019), list multiple therapeutic regimens that may be used for primary therapy and previously treated multiple myeloma.[6] Ninlaro/Revlimid/dexamethasone is an Other recommended regimen (transplant and non-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/cyclophosphamide/dexamethasone, Ninlaro/dexamethasone, and Ninlaro/Pomalyst/dexamethasone. NCCN guidelines for systemic light chain amyloidosis (version 1.2020, December 6, 2019) list Ninlaro ± dexamethasone among the treatment options for patients who have relapsed/refractory disease.[7] NCCN guidelines for Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma list Ninlaro/rituximab/dexamethasone among the treatment options for primary therapy.[8]

Safety

As a class, the PIs are distinct in their specificities and affinities; thus, safety profiles differ within the class. Looking at the Warnings/Precautions for the PIs, thrombocytopenia and embryofetal toxicity are a concern for all of these agents (Ninlaro, Velcade® [bortezomib injection], and Kyprolis® [carfilzomib intravenous

{IV} infusion]).[1,3-4] However, peripheral edema and cutaneous reactions are specific to Ninlaro, gastrointestinal toxicities and peripheral neuropathy are a concern for Ninlaro and Velcade, and hepatotoxicity is listed for Ninlaro and Kyprolis.

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

93. Multiple Myeloma. Approve for 3 years if the patient meets at least ONE of the following conditions (A, B, or C):
- **91.** Ninlaro will be taken in combination with Revlimid (lenalidomide capsules) and dexamethasone; OR
- **92.** The patient has received at least ONE prior regimen for multiple myeloma.
  Note: Examples include regimens containing Velcade (bortezomib injection), Kyprolis (carfilzomib infusion), Revlimid (lenalidomide capsules), Darzalex (daratumumab injection).); OR
- **93.** The agent will be used following autologous stem cell transplantation (ASCT).

Other Uses with Supportive Evidence

94. Systemic Light Chain Amyloidosis. Approve for 3 years if the 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.

95. Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma. Approve for 3 years if used in combination with a rituximab product and dexamethasone.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Ninlaro 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.)

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

257. Ninlaro® capsules [prescribing information]. Cambridge, MA: Takeda Pharmaceutical Company Limited; November 2016.
258. Moreau P, Richardson PG, Cavo M, et al. Proteasome inhibitors in multiple myeloma: 10 years later. *Blood*. 2012;120(5):947-959.

259. Velcade injection [prescribing information]. Cambridge, MA: Millennium Pharmaceuticals; June 2017.
260. Kyprolis injection [prescribing information]. Thousand Oaks, CA: Onyx Pharmaceuticals/Amgen; September 2018.
261. American Cancer Society. Multiple myeloma. Last updated: January 8, 2020. Available at: http://www.cancer.org/cancer/multiplemyeloma/detailedguide/multiple-myeloma-key-statistics. Accessed on February 17, 2020.
262. 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 February 17, 2020.
263. The NCCN Systemic Light Chain Amyloidosis Clinical Practice Guidelines in Oncology (Version 1.2020 – December 6, 2019). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 13, 2020.
264. The NCCN Waldenstrom Macroglobulinemia/Lymphoblastic Lymphoma Clinical Practice Guidelines in Oncology (Version 1.2020 – December 6, 2019). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 13, 2020.

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:

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
268. Nubeqa® [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceutical Inc.; July 2019.
269. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Odomzo® (sonidegib capsules – Novartis)

REVIEW DATE: 10/16/2019

OVERVIEW
Odomzo, a hedgehog pathway inhibitor, is indicated for the treatment of adults with locally advanced basal cell carcinoma (BCC) 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.

Disease Overview
Localized BCC is most commonly treated with surgery or radiation therapy and is usually cured by local therapy.[2] Few options exist in the scenario of disease progression; however, hedgehog pathway inhibitors have provided another option for patients with advanced disease and in those who are not amenable to local therapy. The sonic hedgehog signaling pathway has emerged as playing a pivotal role in the parthenogenesis of BCC.[2] Mutations in the patched (PTCH) gene on chromosome 9q, which codes for the sonic hedgehog receptor, are the underlying cause of nevoid BCC syndrome, and are frequently present in sporadic BCC.

Guidelines
National Comprehensive Cancer Network (NCCN) guidelines for BCC (version 1.2019 – August 31, 2018) 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] or clinical trials should be considered.

Other Uses with Supportive Evidence

Although Odomzo is not indicated in metastatic BCC, 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 BCC list hedgehog pathway inhibitors (i.e., Erivedge, Odomzo) as treatment options for patients with metastatic BCC.[2]

Safety

Odomzo has a Boxed Warning stating that it may cause fetal harm when administered to a pregnant woman.[1] Pregnancy status should be verified prior to initiation of therapy. Female patients should use contraception during and for 24 months after the final dose. Male patients should use contraception to avoid exposure to a partner of childbearing potential during and for 8 months after the final dose.

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

96. Basal Cell Carcinoma (BCC), Locally Advanced. Approve for 3 years if the patients meets ONE of the following conditions (A or B):

~~**94.**~~ Initial Therapy. Approve if the patient meets ONE of the following (i or ii):

- **i.** The patient's basal cell carcinoma has recurred following surgery or radiation therapy; OR
- **ii.** The patient meets BOTH of the following (a and b):
  - ~~**a)**~~ The patient is not a candidate for surgery; AND
  - ~~**b)**~~ According to the prescribing physician, the patient is not a candidate for radiation therapy.

95. Patients Currently Receiving Odomzo. Approve.

Other Uses with Supportive Evidence

97. Basal Cell Carcinoma (BCC), Metastatic. Approve for 3 years.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Odomzo 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.)

39. 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.

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

265. Odomzo® capsules [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; May 2019.
266. The NCCN Basal Cell Skin Cancers Clinical Practice Guidelines in Oncology (Version 1.2019 – August 31, 2018). © 2017 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 23, 2019.
267. 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.
268. Erivedge® capsules [prescribing information]. South San Fransisco, CA: Genentech/Roche; February 2019.
269. 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.
270. 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.

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

16. 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
3. Pemazyre™ tablets [prescribing information]. Wilmington, DE: Incyte Corporation; April 2020.
4. 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.

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

17. 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
5. Piqray® tablets [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation.; May 2019.
6. 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.
7. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Pomalyst® (pomalidomide capsules – Celgene)

DATE REVIEWED: 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

98. Multiple Myeloma. Approve for 3 years.

99. 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

100. Central Nervous System (CNS) Lymphoma. Approve for 3 years if the patient has relapsed or refractory disease.

101. Systemic Light Chain Amyloidosis. Approve for 3 years.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Pomalyst 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.)

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

270. Pomalyst® capsules [prescribing information]. Summit, NJ: Celgene; May 2020.
271. 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.
272. 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.
273. 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.
274. 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.
275. 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.
276. 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.

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 thse who meet the following criteria:

FDA-Approved Indications

18. 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.

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
8. Qinlock™ tablets [prescribing information]. Waltham, MA: Deciphera Pharmaceuticals, LLC; May 2020.
9. 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.

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

19. 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.

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
10. Retevmo™ capsules [prescribing information]. Indianapolis, IN: Eli Lilly and Company; May 2020.
11. 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.
12. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Revlimid® (lenalidomide capsules – Celgene)

DATE REVIEWED: 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 3 years in duration.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

102. 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).

103. Mantle Cell Lymphoma. Approve for 3 years.

104. Marginal Zone Lymphoma. Approve for 3 years.

105. Multiple Myeloma. Approve for 3 years.

106. 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

107. 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.

108. Castleman's Disease. Approve for 3 years in patients with relapsed/refractory or progressive disease.

109. Central Nervous System (CNS) Cancer (Primary). Approve for 3 years if according to the prescriber the patient has relapsed or refractory disease.

110. 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.

111. 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.

112. 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.

113. 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.

114. Systemic Light Chain Amyloidosis. Approve for 3 years.

115. 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

Revlimid 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.)

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

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272. 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.
273. 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 March 13, 2020.
274. 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.
275. 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 13, 2020.
276. The NCCN Hodgkin Lymphoma Clinical Practice Guidelines in Oncology (Version 1.2020 – January 30, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 13, 2020.
277. 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.
278. 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.
279. 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.
280. The NCCN Central Nervous System Cancers Guidelines in Oncology (Version 1.2020 – March 10, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 13, 2020.

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:

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
281. Rozlytrek™ capsules [prescribing information]. South San Francisco, CA: Genetech; August 2019.
282. The NCCN Drugs & Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed August 24, 2020. Search terms: entrectinib.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Rubraca™ (rucaparib tablets – Clovis Oncology)

DATE REVIEWED: 02/19/2020; 05/27/2020 selected revision

OVERVIEW

Rubraca, a poly (ADP-ribose) polymerase (PARP) inhibitor, is indicated[1]:

A) For the **treatment** of adult patients with deleterious *BReast CAncer (BRCA)* mutation (germline and/or somatic) associated epithelial **ovarian, fallopian tube, or primary pertitoneal cancer** who have been treated with two or more chemotherapies;

B) For the **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;

C) Treatment of adult patients with a deleterious *BRCA* mutation (germline and/or somatic)-associated **metastatic castration-resistant prostate cancer** (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy.

Guidelines

According to the National Comprehensive Cancer Network (NCCN) guidelines for ovarian cancer (version 3. 2019 – November 26, 2019), 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).

The NCCN prostate cancer guidelines (version 2.2020 – May 21, 2020) 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

116. Ovarian, Fallopian Tube, or Primary Peritoneal Cancer – Treatment.
- **A)** Initial Therapy. Approve for 3 years if the patient meets the following criteria (i and ii):
  - **i.** The patient has a *BRCA*-mutation (germline or somatic) as confirmed by an approved test; AND
  - **ii.** The patient has progressed on two or more prior lines of chemotherapy.
- **B)** 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 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, and D):
- **A)** The patient has metastatic disease that is *BRCA*-mutation positive (germline and/or somatic); AND
- **B)** The patient meets one of the following criteria (i or ii):
  - **i.** 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
  - **ii.** The patient has had a bilateral orchiectomy; AND
- **C)** The patient has been previously treated with at least one androgen receptor-directed therapy.
  Note: Examples are abiraterone, Xtandi (enzalutamide tablets), Yonsa® (abiraterone acetate tablets); AND
- **D)** The patient meets one of the following criteria (i or ii):
  - **i.** The patient has been previously treated with at least one taxane-based chemotherapy.
    Note: Examples are docetaxel, cabazitaxel; OR
  - **ii.** The patient is not a candidate or is intolerant to taxane-based chemotherapy, according to the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Rubraca 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.)

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
359. Rubraca™ tablets [prescribing information]. Boulder, CO: Clovis Oncology, Inc.; May 2020.
360. List of cleared or approved companion diagnostic devices (*in vitro* and imaging tools). U.S. Food and Drug Administration. Available at: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm. Last updated 12/22/2016. Accessed on January 18, 2018.
361. The NCCN Ovarian Cancer Clinical Practice Guidelines in Oncology (Version 3.2019 – November 26, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed February 14, 2020.
362. 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 May 23, 2020.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Rydapt® (midostaurin capsules – Novartis)

DATE REVIEWED: 02/05/2020

OVERVIEW
Rydapt is a tyrosine kinase inhibitor (TKI) indicated in combination with standard cytarabine + daunorubicin induction and cytarabine consolidation chemotherapy, for the treatment of adults with newly diagnosed acute myeloid leukemia (AML) who are FMS-like tyrosine kinase 3 (*FLT3*) mutation-positive, as detected by an FDA-approved test.[1] Rydapt is not indicated as a single-agent induction therapy for the treatment of patients with AML. Rydapt is also indicated for the treatment of adults with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL).

AML
FLT3 Mutation
The prognosis of AML is worse for patients with *FLT3* mutations which comprise approximately 30% to 40% of AML cases.[4] 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.

General Treatment of AML
Treatment of acute leukemia is divided into induction chemotherapy and post-remission (consolidation) therapy.[4] Most initial treatment decisions for AML are based on age (≥ 60 years of age vs. < 60 years of age), history of prior myelodysplasia or cytotoxic therapy, and performance status. The standard induction chemotherapy used for the treatment of AML (in patients < 60 years of age) consists of cytarabine and an anthracycline (either daunorubicin or idarubicin) administered via intravenous infusion (IV) infusion; Rydapt is the first oral targeted therapy indicated for *FLT3*-mutated AML. Many different therapies are recommended.

Guidelines
The Comprehensive Cancer Network (NCCN) guidelines on AML (version 3.2020 – December 23, 2019), recommend Rydapt + IV chemotherapy among the treatment options for induction, re-induction, and post-remission therapy.[4] For treatment indication for patients < 60 years of age, a recommended regimen includes standard-dose cytarabine (200 mg/m^2 continuous infusion) x 7 days + daunorubicin (60 mg/m^2) x 3 days + Rydapt (50 mg Q12H) on Days 8 to 21 in FLT3-mutated AML (category 2A). 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. After standard-dose cytarabine induction/re-induction in patients < 60 years of age, treatment is based on the results of follow-up bone marrow biopsy. In patients with significant residual disease without hypocellular marrow a recommended regimen includes standard-dose cytarabine + daunorubicin + Rydapt. In patients with significant cytoreduction, the guidelines recommend various regimens including standard-dose cytarabine + daunorubicin + Rydapt. In patients < 60 years of age with intermediate-risk cytogenetics and/or molecular abnormalities, or treatment-related disease other than core binding factor and/or poor risk cytogenetics and/or molecular abnormalities, an option cited is high-dose cytarabine (HiDAC) 1.5 to 3 g/m^2 over 3 hours once every 12 hours on Days 1, 3, 5, or 1, 2, 3 with Rydapt 50 mg once every 12 hours on Days 8 to 21 (FLT3-mutatated AML. Patients ≥ 60 years of age who are candidates for intensive remission induction therapy, for those with intermediate risk cytogenetics and FLT3 mutant, cytarabine + daunorubicin _ In patients ≥ 60 years of age, after standard-dose cytarabine one of the recommended regimens is standard-dose cytarabine + daunorubicin + Rydapt. Post-remission therapy in patients ≥ 60 years of age is based on the type of prior therapy received. For patients who previously received intensive therapy, and who are in remission with a complete response one cited regimens includes intermediate-dose cytarabine + Rydapt.

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.

The NCCN has guidelines for systemic mastocytosis (version 2.2019 – September 20, 2018).[11] 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

117. Acute Myeloid Leukemia (AML). Approve for 3 years if the patient meets the following criteria (A and B)
- **A)** The patient is *FLT3*-mutation positive AML as detected by an approved test; AND
- **B)** The 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.

118. Aggressive Systemic Mastocytosis (ASM). Approve for 3 years.

119. Systemic Mastocytosis Associated with Acute Hematologic Neoplasm (SM-AHN). Approve for 3 years.

120. Mast Cell Leukemia (MCL). Approve for 3 years.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Rydapt 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.)

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

277. Rydapt® capsules [prescribing information]. East Hanover, NJ: Novartis; July 2019.
278. Stone RM, Mandrekar S, Laumann K, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with FLT3 mutation. *N Engl J Med*. 2017;377:454-464.
279. 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 January 31, 2020.
280. Pardanani A. Systemic mastocytosis in adults: 2019 update on diagnosis, risk stratification and management. *Am J Hematol*. 2019;94(3):363-377.
281. Gotlib J, Kluin-Nelemans. HC, George TI, et al. Efficacy and safety of midostaurin to advanced systemic mastocytosis. *N Engl J Med*. 2016;374(26): 2530-2541
282. DeAngelo DJ, George TJ Linder A, et al. Efficacy and safety of midostaurin in patients with advanced systemic mastocytosis: 10-year median follow-up of a phase II trial. *Leukemia*. 2018;32:470-478.
283. Van Anrooij B, Oude Elberink JNG, Span LF, et al. Midostaurin in indolent systemic mastocytosis patients: an open-label phase 2 trial. *J Allergy Clin Immunol*. 2018;142(3):1006-1008.
284. Kim ES. Midostaurin: first global approval. *Drugs*. 2017;77:1251-1259.
285. Scherber RM, Borate U. How we diagnose and treat systemic mastocytosis in adults. *Br J Haematol*. 2018;180(1):11-23.
286. Kasamon Y, Ko CW, Subramaniam S, et al. FDA approval summary: midostaurin for the treatment of advanced systemic mastocytosis. *Oncologist*. 2018;23:1511-1519.
287. 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 January 31, 2020.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Sprycel® (dasatinib tablets – Bristol-Myers Squibb)

DATE REVIEWED: 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 3 years in duration.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

20. Acute Lymphoblastic Leukemia (ALL) That is Philadelphia Chromosome Positive (Ph+). Approve for 3 years.

21. 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

Sprycel 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.)

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

283. Sprycel® tablets [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; December 2018.
284. Gleevec® tablets [prescribing information]. East Hanover, NJ: Novartis; July 2018.
285. Tasigna® capsules [prescribing information]. East Hanover, NJ: Novartis; September 2019.
286. Bosulif® tablets [prescribing information]. New York, NY: Pfizer Inc; October 2019.
287. Iclusig® tablets [prescribing information]. Cambridge, MA: Ariad Pharmaceuticals; January 2020.
288. 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.
289. 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.
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291. 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.
292. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Stivarga® (regorafenib tablets – Bayer HealthCare Pharmaceuticals, Inc.)

DATE REVIEWED: 01/29/2020

OVERVIEW

Stivarga, a kinase inhibitor, is indicated for the treatment of patients with the following conditions:[1]

1. Metastatic colorectal cancer (mCRC) 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. Locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treatment with Gleevec® (imatinib mesylate tablets) and Sutent® (sunitinib malate capsules);
3. Hepatocellular carcinoma (HCC) who have been previously treated with Nexavar® (sorafenib tablets).

Stivarga is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, metastasis, and tumor immunity. In *in vitro* biochemical or cellular assays, Stivarga (or its major active metabolites) inhibited the activity of various receptors, some of which include vascular endothelial growth factor receptor (VEGFR)1, VEGFR2, VEGFR3, platelet-derived growth factor receptor (PDGFR)-alpha, PDGFR-beta, fibroblast growth factor receptor (FGFR)1, FGFR2, BRAF, $BRAF^{V600E}$, and Abl at concentrations of Stivarga that have been achieved clinically.

Guidelines

Colon and/or Rectal Cancer

The National Comprehensive Cancer Network (NCCN) guidelines on colon cancer (version 4.2019 – November 8, 2019) and rectal cancer (version 3.2019 – September 26, 2019) recommend Stivarga as subsequent therapy as a single agent for unresectable advanced or metastatic disease not previously treated with Stivarga for the following uses: for first progression (*KRAS/NRAS* mutant only) or second progression for disease previously treated with FOLFOXIRI (5-fluorouracil/leucovorin, irinotecan, oxaliplatin) regimen with or without bevacizumab, for second progression for disease previously treated with fluoropyrimidine-, irinotecan- and oxaliplatin-based regimens, or for progression for disease that progressed through all available regimens, including Lonsurf® (trifluridine and tipiracil tablets). Stivarga may be given before or after Lonsurf.[2,3]

Hepatocellular Carcinoma

The NCCN clinical practice guidelines on hepatobiliary cancers (version 3.2019 – August 1, 2019) 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 soft tissue sarcoma guidelines (version 4.2019 – September 12, 2019) recommend Stivarga (category 1) for treatment of progressive GIST disease when the patient is no longer receiving benefit from Gleevec or Sutent.[4] If disease is progressing despite prior therapy with imatinib (Gleevec® tablets, generics) or Sutent® (sunitinib capsules), the following options may be considered: Stivarga (category 1), clinical trial, or best supportive care. Discontinuing tyrosine kinase inhibitor (TKI) therapy (i.e., imatinib, Sutent, or Stivarga) even with progressive disease may accelerate the pace of disease progression and worsen symptoms. In patients with GIST progressing despite imatinib, Sutent, and Stivarga, other options may be considered or a previously tolerated and effective TKI may be restarted for palliation of symptoms. Stivarga, imatinib, or Sutent can be used in combination with Afinitor® (everolimus tablets). Continuation of life-long TKI therapy should be considered for palliation of symptoms as part of best supportive care.

The NCCN soft tissue sarcoma guidelines (version 4.2019 – September 12, 2019) recommend Stivarga (all category 2A) as single-agent palliative therapy for patients with: 1) non-adipocytic extremity/superficial

trunk, head/neck sarcoma with stage IV or recurrent disease with disseminated metastases, 2) non-adipocytic retroperitoneal/intra-abdominal sarcoma with unresectable or progressive disease, or 3) pleomorphic rhabdomyosarcoma.[4,6]

The NCCN bone cancer guidelines (version 1.2020 – August 12, 2019) 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]

Safety

Stivarga has Boxed Warnings concerning risks of hepatotoxicity.[1] Hepatic function should be monitored prior to and during treatment. Depending on severity and persistence, therapy with Stivarga should be interrupted and then reduced or discontinued for hepatotoxicity manifested by elevated liver function tests or hepatocellular necrosis.

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

121. Colon and Rectal Cancer. Approve for 3 years if the patient meets the following criteria (A, B, C, D, and E):
- **96.** Patient has metastatic disease; AND
- **97.** Patient has been previously treated with a fluoropyrimidine (e.g., capecitabine, 5-fluorouracil [5-FU]); AND
- **98.** Patient has been previously treated with oxaliplatin; AND
- **99.** Patient has been previously treated with irinotecan; AND
- **100.** 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 the following criteria (A, B, and C):
- **A)** Patient has 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. Soft Tissue Sarcoma. Approve for 3 years if the patient meets one of the following criteria (A or B):
- **A)** The patient has non-adipocytic extremity/superficial trunk, head/neck, or retroperitoneal/intra-abdominal sarcoma, OR
- **B)** The patient has pleomorphic rhabdomyosarcoma.

5. Osteosarcoma. Approve for 3 years if the patient meets one of the following criteria (A and B):
- **A)** The patient has relapsed/refractory or metastatic disease; AND
- **B)** Stivarga is used as subsequent therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Stivarga 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.

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

1. Stivarga® tablets [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; June 2018.
2. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 4.2019 – November 8, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 18, 2019.
3. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (Version 3.2019 – September 26, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 26, 2019.
4. The NCCN Soft Tissue Sarcoma Practice Guidelines in Oncology (Version 4.2019 – September 12, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 18, 2019.
5. The NCCN Hepatobiliary Cancers Practice Guidelines in Oncology (Version 3.2019 – August 1, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 18, 2019.
6. The NCCN Drugs and Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 18, 2019. Search term: regorafenib.
7. 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 December 18, 2019.

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).

122. **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.

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
293. Sutent® capsules [prescribing information]. New York, NY: Pfizer; May 2019.
294. 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.

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

22. 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.

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

13. Tabrecta™ tablets [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; May 2020.
14. 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.

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

363. Tafinlar® capsules [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; April 2020.
364. 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.
365. 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.
366. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Tagrisso® (osimertinib tablets – AstraZeneca)

DATE REVIEWED: 12/18/2019

OVERVIEW

Tagrisso, a kinase inhibitor, is indicated for the treatment of patients with metastatic epidermal growth factor receptor (*EGFR*) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test.[1] It is specifically approved for patients who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy (EGFR-TKI). Tagrisso is also indicated for the 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.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for NSCLC (version 1.2020 – November 6, 2019) recommend *EGFR* mutation testing in patients with nonsquamous NSCLC (i.e., adenocarcinoma, large cell) or in NSCLC not otherwise specified (NOS).[2] Tarceva® (erlotinib tablets), 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

123. Non-Small Cell Lung Cancer (NSCLC) – Epidermal Growth Factor Receptor (*EGFR*) Mutation-Positive. Approve for 3 years if the patient meets ONE of the following criteria (A or B):
- **A)** The patient meets BOTH of the following criteria (i and ii):
  - **i.** The patient has metastatic *EGFR* T790M mutation-positive NSCLC as detected by an approved test; AND
  - **ii.** The patient has progressed on one of the EGFR-tyrosine kinase inhibitors (e.g., Tarceva® [erlotinib tablets], Iressa® [gefitinib tablets], Vizimpro® [dacomitinib tablets], Gilotrif® [afatinib tablets]); OR
- **B)** The patient has metastatic NSCLC and meets ONE of the following criteria (i or ii):
  - **i.** The patient has *EGFR* exon 19 deletions as detected by an approved test; OR
  - **ii.** The patient has *EGFR* exon 21 L858R mutations as detected by an approved test.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Tagrisso 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.)

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
367. Tagrisso™ tablets [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; April 2018.
368. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 1.2020 – November 6, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 15, 2019.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Talzenna™ (talazoparib capsules – Pfizer)

REVIEW DATE: 10/30/2019

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] Talzenna was approved with an FDA-approved companion diagnostic test.

GUIDELINES
The National Comprehensive Cancer Network (NCCN) guidelines on breast cancer (version 3.2019 – September 6, 2019) 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.

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.** The patient has locally-advanced or metastatic breast cancer; AND
   - **B.** The patients has germline *BRCA* mutation-positive disease; AND
   - **C.** The patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Talzenna 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.

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
369. Talzenna™ capsules [prescribing information]. New York, NY: Pfizer; October 2018.
370. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 3.2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on.October 27, 2019.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Targretin® (bexarotene capsule – Valeant, generics)

REVIEW DATE: 09/25/2019

OVERVIEW

Bexarotene capsule is indicated for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma (CTCL) 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

T-cell lymphoma accounts for approximately 15% of all non-Hodgkin lymphoma (NHL) in the US.[2] CTCL is one of the most common forms of T-cell lymphoma.[2,3]

The most common type of CTCL is mycosis fungoides and its variants, which accounts for approximately 50% to 70% of all CTCLs.[4] 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 2.2019 – December 17, 2018) provide treatment recommendations for the different types of CTCLs.[2] Bexarotene capsules are listed as one of the therapies within the Systemic Category A drugs. The Systemic Category A drugs are typically used before Systemic Category B or C drugs.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of bexarotene capsules. 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. All approvals are provided for 3 years in duration unless otherwise noted below.

Automation: None.

Recommended Authorization Criteria
Coverage of bexarotene capsule is recommended in those who meet the following criteria:

FDA-Approved Indications

124. Cutaneous T-Cell Lymphoma (CTCL) – Cutaneous Manifestations. Approve bexarotene capsule for 3 years if the patient meets the following criteria (A and B):
- **X)** Bexarotene capsule is prescribed by, or in consultation with, an oncologist or a dermatologist; AND
- **Y)** 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
Bexarotene capsules 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 conditions not included in the Recommended Authorization Criteria.

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
295. Targretin® capsule [prescribing information]. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC; July 2015.
296. Cutaneous T-cell lymphoma. Available at: http://www.lymphoma.org/site/pp.asp?c=bkLTKaOQLmK8E&b=6300151. Accessed on September 19, 2019.
297. The NCCN Primary Cutaneous Lymphomas Clinical Practice Guidelines in Oncology (Version 2.2019 – December 17, 2018). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 19, 2019.
298. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Targretin® (bexarotene gel 1% – Valeant)

REVIEW DATE: 09/25/2019

OVERVIEW
Targetin gel is indicated for the topical treatment of cutaneous lesions in patients with cutaneous T-cell lymphoma (CTCL) [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

T-cell lymphoma accounts for approximately 15% of all non-Hodgkin lymphoma (NHL) in the US.[2] CTCL is one of the most common forms of T-cell lymphoma.[2,3]

The most common type of CTCL is mycosis fungoides and its variants, which accounts for approximately 50% to 70% of all CTCLs.[4] 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 2.2019 – December 17, 2018) provide treatment recommendations for the different types of CTCLs.[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. 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. All approvals are provided for 3 years in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

125. Cutaneous T-Cell Lymphoma (CTCL) – 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

Targretin gel 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 conditions not included in the Recommended Authorization 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
299. Targretin® gel [prescribing information]. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC; October 2016.
300. Cutaneous T-cell lymphoma. Available at: http://www.lymphoma.org/site/pp.asp?c=bkLTKaOQLmK8E&b=6300151. Accessed on September 19, 2019.
301. The NCCN Primary Cutaneous Lymphomas Clinical Practice Guidelines in Oncology (Version 2.2019 – December 17, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 19, 2019.
302. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Tasigna® (nilotinib capsules – Novartis)

DATE REVIEWED: 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 3 years in duration.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

23. Chronic Myeloid Leukemia (CML) That is Philadelphia Chromosome Positive (Ph+). Approve for 3 years.

Other Uses with Supportive Evidence

24. 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).

25. Gastrointestinal Stromal Tumor (GIST). Approve for 3 years if the patient meets the following criteria (A, B, and C):
D) Patient has tried Gleevec® (imatinib tablets); AND
E) Patient has tried Sutent® (sunitinib capsules); AND
F) Patient has tried Stivarga® (regorafenib tablets).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Tasigna 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.)

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

303. Tasigna® capsules [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals, Inc.; September 2019.
304. Gleevec® tablets [prescribing information]. East Hanover, NJ: Novartis; July 2018.
305. Sprycel® tablets [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; December 2018.
306. Bosulif® tablets [prescribing information]. New York, NY: Pfizer Inc; October 2019.
307. Iclusig® tablets [prescribing information]. Cambridge, MA: Takeda/Ariad Pharmaceuticals; January 2020.

308. 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.
309. 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.
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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Tazverik Prior Authorization Policy
- Tazverik™ (tazemetostat tablets – Epizyme)

REVIEW DATE: 01/29/2020; selected revision 06/24/2020

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
The National Comprehensive Cancer Network (NCCN) guidelines for soft tissue sarcoma (version 6.2019 – February 10, 2020) have been updated to recommend Tazverik 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).

NCCN guidelines for B-cell lymphomas (version 2.2020 – July 9, 2020) 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 in patients who have no satisfactory alternative treatment options.[3]

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

140. 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.

141. 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)** Patient's 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:

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

531. Tazverik [prescribing information]. Cambridge, MA: Epizyme; June 2020.
532. 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 10, 2020.
533. 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 July 10, 2020.

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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Thalomid® (thalidomide capsules – Celgene)

DATE REVIEWED: 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.)

54. 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]

55. 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.

56. 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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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Tibsovo® (ivosidenib tablets – Agios)

DATE REVIEWED: 02/05/2020

OVERVIEW

Tibsovo, an isocitrate dehydrogenase-1 (IDH1) inhibitor, is indicated for the treatment of acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test in adults with newly diagnosed AML who are ≥ 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy and in adults with relapsed or refractory AML.[1] The recommended dose is 500 mg orally once daily (QD) with or without food until disease progression or unacceptable toxicity. Do not administer with a high-fat meal.

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.[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 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).[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.[3] Various gene mutations are present in adults with AML.[2,3] The incidence of IDH1 mutations have been reported in 6% to 9% of AML cases.[2]

Clinical Efficacy

The efficacy of Tibosovo was assessed in an open-label, single-arm, multicenter, clinical study involving 174 adult patients with relapsed or refractory AML that had an IDH1 mutation.[1,4] Patients were assigned to receive Tibosovo 500 mg QD. The median patient age was 67 years.[1,4] The most common types of IDH1 mutation were R132C and R132H.[1] Patients had received a median of two prior therapies (range, 1 to 6).[4] Approximately 70% and 64% of patients had received prior intensive chemotherapy and non-intensive chemotherapy, respectively.[4] Efficacy was based on the rate of complete remission (CR) plus complete remission with partial hematologic recovery (CRh), the duration of CR+CRh, and the rate of conversion from transfusion dependence to transfusion independence.[1] The median follow-up was 8.3 months (range, 0.2 to 39.5 months) and the median treatment duration was 4.1 months (range, 0.1 to 39.5 months). CR (defined as < 5% blasts in the bone marrow, no evidence of disease and full recovery of peripheral blood counts [platelets > 100,000/microliter and absolute neutrophil counts > 1,000/microliter]) was achieved by 24.7% of patients (n = 43/174). Approximately 8% of patients (n = 14/174) obtained complete remission with partial hematological recovery (defined as < 5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts [platelets > 50,000/microliter and absolute neutrophil count > 500/microliter]). For patients who obtained CR or CRh, the median time first response was 2 months (range, 0.6 to 5.6 months). For the 110 patients who were dependent upon red blood cell (RBC) and/or platelet transfusions at baseline, 37.3% of patients (n = 41/110) became independent of RBC and platelet transfusions during any 56-day post-baseline period. The efficacy of Tibsovo was assessed in an open-label, single-arm, multicenter trial that included patients (n = 28) with newly-diagnosed AML and an IDH1 mutation.[1] The cohort included patients ≥ 75 years old who had comorbidities that precluded the use of intensive induction chemotherapy based on a variety of reasons (e.g., severe cardiac or pulmonary disease). The median follow-up was 8.1 months (range, 0.6 to 40.9 months) and the median treatment duration was 4.3 months (range, 0.3 to 40.9 months). The complete remission rate was 28.6%.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on AML (version 3.2020 – December 23, 2019), are extensive.[2] Tibsovo is recommended for patients who have relapsed or refractory disease who have the IDH1 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 with the IHD1 mutation. In patients ≥ 60 years of age who had a response to previous lower intensity therapy, Tibsovo can be continued. Both clinical scenarios apply to patients who are IDH1 mutation positive.

Safety

Tibsovo has a Boxed Warning regarding differentiation syndrome.[1] Other more common adverse events (AEs) were fatigue (39%), leukocytosis (38%), arthralgia (36%), diarrhea (34%), dyspnea (33%), edema (32%), nausea (31%), mucositis (28%), electrocardiogram QT prolongation (26%), rash (26%), pyrexia (23%), cough (22%), and constipation (20%). 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

126. Acute Myeloid Leukemia (AML). Approve for 3 years if the disease is isocitrate dehydrogenase-1 (IDH1) mutation positive as detected by an approved test.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Tibsovo 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.)

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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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

26. 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.

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
15. Tukysa™ tablets [prescribing information]. Bothell, WA: Seattle Genetics, Inc.; April 2020.
16. 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.

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:

58. 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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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Tykerb® (lapatinib ditosylate tablets – Novartis Pharmaceuticals)

REVIEW DATE: 12/18/2019

OVERVIEW

Tykerb is indicated in combination with capecitabine tablets for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress human epidermal growth factor receptor 2 (HER2) and who have received prior therapy including an anthracycline, a taxane, and Herceptin® (trastuzumab intravenous injection).[1] *Limitation of use*. Patients should have disease progression on Herceptin prior to initiation of treatment with Tykerb in combination with capecitabine tablets. Tykerb is also indicated in combination with letrozole tablets for the treatment of postmenopausal women with hormone receptor-positive (HR+) metastatic breast cancer that overexpresses HER2 for whom hormonal therapy is indicated. Tykerb in combination with an aromatase inhibitor (AI) has not been compared to a Herceptin-containing chemotherapy regimen for the treatment of metastatic breast cancer. Tykerb is a kinase inhibitor of the intracellular tyrosine kinase domains of both epidermal growth factor receptor (*EGFR*) and of HER2 (ErbB2) receptors. Tykerb inhibits ErbB-driven tumor cell growth *in vitro* and in various animal models.

Guidelines

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines on breast cancer (version 3.2019 – September 6, 2019) recommend Tykerb 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]

Tykerb 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 guidelines for bone cancer (version 1.2020 – August 12, 2019) and the compendium recommends the use of Tykerb for *EGFR*-positive recurrent disease.[3,5]

The NCCN clinical practice guidelines on central nervous system (CNS) cancers (version 3.2019 – October 18, 2019) recommend treatments for patients with brain metastases from breast cancer.[3,4] Capecitabine with or without Tykerb 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 Tykerb is active against the primary tumor (breast).

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 Tykerb is recommended in those who meet the following criteria:

FDA-Approved Indications

27. 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.** The patient has received prior therapy with trastuzumab AND Tykerb will be used in combination with capecitabine; OR
  - **ii.** Tykerb 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)** The patient is a postmenopausal woman;* OR
    - **b)** The patient is a premenopausal or perimenopausal woman* and is receiving ovarian suppression/ablation with a gonadotropin-releasing hormone (GnRH) agonist (e.g., Lupron® [leuprolide], Trelstar® [triptorelin], Zoladex® (goserelin]), surgical bilateral oophorectomy, or ovarian irradiation; OR
    - **c)** The patient is a man* and is receiving a gonadotropin-releasing hormone (GnRH) agonist (e.g., Lupron [leuprolide], Trelstar [triptorelin], Zoladex (goserelin]) AND
  - **ii.** Tykerb 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)** The 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)** The patient has not been previously treated with a HER2-inhibitor.
  Note: Examples of HER2-inhibitors are Tykerb, trastuzumab products, Nerlynx (neratinib tablets), Kadcyla (ado-trastuzumab emtansine for injection), Perjeta (pertuzumab for injection).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Tykerb 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.)

59. **Cervical Cancer.** In one Phase II study (n = 228), Tykerb plus Votrient® (pazopanib tablets) was compared with Tykerb 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. Tykerb monotherapy, and the combination arm was discontinued. The median PFS was shorter among Tykerb-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. Tykerb (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.

60. **Gastric, Esophageal, or Gastroesophageal Adenocarcinoma Cancer.** In one Phase II study (n = 47), Tykerb 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 Tykerb 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 Tykerb plus paclitaxel vs. 8.9 months with paclitaxel alone (P = 0.1044). There was no significant difference between Tykerb 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 Tykerb 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 Tykerb 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 Tykerb and placebo, respectively (HR 0.91; 95% CI: 0.73, 1.12). Preplanned exploratory analysis showed OS in the Tykerb was prolonged in Asian and younger patients.

61. **Head and Neck, Squamous Cell Carcinoma.** In one Phase III study in 688 patients with SCCHN, adding Tykerb to chemoradiotherapy and as maintenance monotherapy was not more effective than placebo in improving disease-free survival or OS.[10]

62. **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, Tykerb 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 Tykerb and hormone therapy, respectively (HR 0.94; P = 0.60).[11] The median OS was 46.9 weeks and 43.1 weeks for Tykerb and hormone therapy, respectively (HR 0.88; P = 0.29).

63. 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 Tykerb or placebo after completing first-line or initial chemotherapy.[12] Median PFS, the primary endpoint, for Tykerb 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).

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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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Valchlor (mechlorethamine gel for topical use – Helsinn Therapeutics)

REVIEW DATE: 10/16/2019

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 2.2019 – December 17, 2018) 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 2.2019 – December 17, 2018) 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

142. 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

143. 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

Valchlor 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.

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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POLICY: Oncology – Venclexta® (venetoclax tablets – AbbVie and Genentech)

DATE REVIEWED: 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. This indication is approved under accelerated approval based on response rates. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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.

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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

127. Chronic Lymphocytic Leukemia (CLL). Approve for 3 years.

128. Small Lymphocytic Lymphoma (SLL). Approve for 3 years.

129. 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

130. 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

Venclexta 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.)

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

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PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Verzenio™ (abemaciclib tablets – Eli Lilly and Company)

DATE REVIEWED: 04/15/2020

OVERVIEW

Verzenio, a cyclin-dependent kinase (CDK) 4/6 inhibitor, is indicated for the following uses:

1. In combination with an aromatase inhibitor (AI) as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer;[1-2]
2. In combination with fulvestrant for the treatment of women with HR+, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.[1,3] Pre/perimenopausal women treated with Verzenio plus Faslodex should be treated with a gonadotropin-releasing hormone (GnRH) agonist according to current clinical practice standards.
3. As monotherapy for the treatment of adult patients with HR+, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.[1,4]

Disease Overview

Based on molecular profiling, breast cancer is classified as HR+ (estrogen receptor positive [ER+] and/or progesterone receptor positive [PgR+]), HER2+, or triple negative (ER-negative, PgR-negative, and HER2-negative).[5-6] Most breast cancers in women (71%) are HR+, HER2-negative; these cancers tend to be slow-growing and less aggressive than other subtypes.[6] HR+, HER2-negative tumors are associated with the most favorable prognosis compared with other subtypes, particularly in the short-term, in part because

expression of hormone receptors is predictive of a favorable response to hormonal therapy. In men, about 85% of breast cancers are ER+ and 70% are PgR+.[7] About 12% of breast cancers are HR+ and HER2+, and tend to be higher grade and more aggressive than HR+ cancers.[6] About 5% of breast cancers are HER2+ and do not express hormone receptors. These cancers tend to be more aggressive than other breast cancers and have a poorer short-term prognosis compared with ER+ breast cancers. About 12% of breast cancers in women are triple negative and have a poorer short-term prognosis than other subtypes.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on breast cancer (version 3.2020 – March 6, 2020) recommend CDK 4/6 inhibitor in combination with fulvestrant for first-line therapy (category 1, preferred regimen) in HR+/HER2-negative recurrent or Stage IV (metastatic) disease.[8] This combination can also be used as second/subsequent-line preferred therapy if CDK4/6 inhibitor was not used previously (category 1). CDK 4/6 inhibitors + aromatase inhibitor is also a preferred regimen in guidelines (category 1, preferred). Verzenio is also recommended as "useful in certain circumstances" as a single agent in HR+, HER2-negative breast cancer after progression on prior endocrine therapy and prior chemotherapy in the metastatic setting (category 2A). The above recommendations for CDK4/6 inhibitors is for use in postmenopausal women or premenopausal women receiving ovarian ablation or suppression. The guidelines recommend 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. In men with breast cancer, tamoxifen is generally used rather than an AI, because the data supporting use of an AI in men are limited.[5] The use of AI therapy with LHRH has been reported. Information is not available using Verzenio in men with breast cancer. However, available real-world data suggest comparable efficacy and safety profiles in men as in women; it is reasonable to recommend CDK4/6 inhibitors in combination with an aromatase inhibitor or fulvestrant, everolimus, and PIK3CA inhibitors to men based on extrapolation of data from studies comprised largely of female participants with advanced breast cancer.

The NCCN guidelines state in a footnote that if there is disease progression on CDK4/6 inhibitor therapy, there are limited data to support an additional line of therapy with another CDK4/6-containing regimen.[8] The limited data are based on a multicenter analysis which evaluated clinical outcomes in patients (n = 58) with HR+/HER2-negative metastatic breast cancer who received Verzenio after disease progression on Ibrance or Kisqali.[9] 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. There are no published data with additional line of therapy with Ibrance or Kisqali, if the patient has progressed on Verzenio.

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

131. Breast Cancer in Postmenopausal Women*. Approve for 3 years if the patient meets the following criteria (A, B, C, and D):

101. Patient has advanced or metastatic hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND

102. Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND

103. The 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) The patient's breast cancer has progressed on at least one prior endocrine therapy. Note: Examples are anastrozole, exemestane, letrozole, tamoxifen, Fareston® [toremifene], exemestane plus everolimus, fulvestrant, everolimus plus fulvestrant or tamoxifen, megestrol acetate, fluoxymesterone, ethinyl estradiol; AND

c) The patient has tried chemotherapy for metastatic breast cancer; AND

D) The patient has not had disease progression while on Verzenio.

***** 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, D, and E):

E) Patient has advanced or metastatic hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}] disease; AND

F) Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND

G) The patient is receiving ovarian suppression/ablation with a gonadotropin-releasing hormone (GnRH) agonist (e.g., Lupron [leuprolide], Trelstar [triptorelin], Zoladex (goserelin]), or has had surgical bilateral oophorectomy or ovarian irradiation; AND

H) 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) The patient's breast cancer has progressed on at least one prior endocrine therapy Note: Examples are anastrozole, exemestane, letrozole, tamoxifen, Fareston® [toremifene], exemestane plus everolimus, fulvestrant, everolimus plus fulvestrant or tamoxifen, megestrol acetate, fluoxymesterone, ethinyl estradiol; AND

c) The patient has tried chemotherapy for metastatic breast cancer; AND

E) Patient has not had disease progression while on Verzenio.

***** 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):

I) Patient has advanced or metastatic hormone receptor positive (HR+) [i.e., estrogen receptor positive {ER+} and/or progesterone receptor positive {PR+}]disease; AND
J) Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
K) The patient meets ONE of the following criteria (i, ii, or iii):
- **i.** The patient meets BOTH of the following conditions (a and b):
  - **a)** The patient is receiving a gonadotropin-releasing hormone (GnRH) agonist (e.g., Lupron [leuprolide], Trelstar [triptorelin], Zoladex [goserelin]); AND
  - **b)** 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)** The patient's breast cancer has progressed on at least one prior endocrine therapy Note: Examples are anastrozole, exemestane, letrozole, tamoxifen, Fareston (toremifene), exemestane plus everolimus, fulvestrant, everolimus plus fulvestrant or tamoxifen, megestrol acetate, fluoxymesterone, ethinyl estradiol; AND
  - **c)** The patient has tried chemotherapy for metastatic breast cancer; AND

D) The patient has not had disease progression while on Verzenio.

***** Refer to the Policy Statement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Verzenio 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.

66. 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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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
314. Vistogard® oral granules [prescribing information]. Rockville, MD: Wellstat Therapeutics; February 2017.
315. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Vitrakvi® (larotrectinib capsules and oral solution – Loxo Oncology/Bayer)

DATE REVIEWED: 12/04/2019

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]

The National Comprehensive Cancer Network (NCCN) Compendium lists the following cancers as recommended uses for Vitrakvi[2]: 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, and pancreatic cancer.

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) The patient's tumor has a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation; AND
B) The 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) The patient meets one of the following criteria (i or ii):
  i. There are no satisfactory alternative treatments; OR
  ii. The patient has disease progression following treatment.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Vitrakvi 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.

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

REFERENCES
316. Vitrakvi® capsules and oral solution [prescribing information]. Stamford, CT: Loxo Oncology, Inc.; November 2018.
317. The NCCN Drugs & Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 27, 2019. Search terms: larotrectinib.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Vizimpro® (dacomitinib tablets – Pfizer Labs)

REVIEW DATE: 10/02/2019

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 7.2019 – August 30, 2019) 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. Tagrisso is noted as the "preferred" option. 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). 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).

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

132. 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):
~~**104.**~~ The patient has *metastatic* NSCLC; AND
~~**105.**~~ The patient meets ONE of the following criteria (i or ii):
i. The patient has epidermal growth factor receptor (EGFR) exon 19 deletion as detected by an approved test; OR
ii. The patient has exon 21 (L858R) substitution mutations as detected by an approved test.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Vizimpro 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.)

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 7.2019 – August 30, 2019) © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed September 27, 2019.

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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

133. 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):
- **G)** Patient has previously tried imatinib (Gleevec® tablets, generics); AND
- **H)** Patient has previously tried Sutent® (sunitinib capsules); AND
- **I)** 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.

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

REFERENCES

318. Votrient® tablets [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; May 2017.
319. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Xalkori® (crizotinib capsules – Pfizer)

DATE REVIEWED: 12/18/2019

OVERVIEW

Xalkori, an oral kinase inhibitor, is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.[1] Xalkori is also FDA-approved for the treatment of patients with metastatic NSCLC whose tumors are ROS1-positive.

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. Local recurrence may occur after initial surgery, with a low risk of distant metastases. 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) NSCLC guidelines (version 1.2020 – November 6, 2019), 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).

The NCCN guidelines for soft tissue sarcoma (version 4.2019) recommend Xalkori as single-agent therapy for the treatment of IMT with ALK translocation (category 2A recommendation).[3,5]

The NCCN T-Cell lymphoma guidelines (version 2.2019) recommend Xalkori use in ALK-positive 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.

Other Uses with Supportive Evidence

3. **Non-Small Cell Lung Cancer (NSCLC) with High Level *MET* Amplification or MET Exon 14 Skipping Mutation.** Approve for 3 years.

4. **Soft Tissue Sarcoma Inflammatory Myofibroblastic Tumor (IMT) with ALK Translocation.** Approve for 3 years.

5. **Peripheral T-Cell Lymphoma – Anaplastic Large Cell Lymphoma (ALCL), ALK-Positive.** Approve for 3 years if Xalkori is used as subsequent therapy for relapsed or refractory disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Xalkori 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.)

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

References

371. Xalkori® capsules [prescribing information]. New York, NY: Pfizer Inc; June 2019.
372. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 1.2020 – November 6, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 15, 2019.
373. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (Version 4.2019 – September 12, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 15, 2019.
374. The NCCN T-Cell lymphomas Clinical Practice Guidelines in Oncology (Version 2.2019 – December 17, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed December 15, 2019.
375. The NCCN Drugs & Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on: December 15, 2019. Search term: crizotinib.

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

134. 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.

70. 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. Xermelo™ tablets [prescribing information]. The Woodlands, TX: Merck; February 2017.
377. 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.

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

144. 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.)

138. 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
538. Xospata® tablets [prescribing information]. Northbrook, IL: Astellas Pharma; May 2019.
539. 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.
540. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Xpovio Prior Authorization Policy
- Xpovio™ (selinexor tablets – Karyopharm Therapeutics, Inc.)

REVIEW DATE: 07/01/2020

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.

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
Guidelines from the National Comprehensive Cancer Network (NCCN) [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] Xpovio/dexamethasone is among the regimens considered useful in certain circumstances for previously treated multiple myeloma, specifically for the approved indication.

NCCN guidelines for B-cell lymphomas (version 2.2020 – July 9, 2020) recommend Xpovio as third-line and subsequent therapy of DLBCL, after at least two lines of systemic therapy.[3] This includes use in patients with disease progression after transplant or chimeric antigen receptor (CAR) T-cell therapy.

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, C, D, and E):
   5. Patient is ≥ 18 years of age; AND
   6. Patient has tried at least two proteasome inhibitors; AND
   Note: Examples include Velcade (bortezomib injection), Kyprolis (carfilzomib infusion), Ninlaro (ixazomib capsules).
   7. Patient has tried at least two immunomodulatory drugs; AND
   Note: Examples include Revlimid (lenalidomide capsules), Pomalyst (pomalidomide capsules), Thalomid (thalidomide capsules).
   8. Patient has tried an anti-CD38 monoclonal antibody; AND
   Note: For example, Darzalex (daratumumab infusion), Darzalex Faspro (daratumumab and hyaluronidase-fihj subcutaneous injection), or Sarclisa (isatuximab-irfc infusion).
   9. The agent will be taken in combination with dexamethasone.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Xpovio is not recommended in the following situations:

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
541. Xpovio [prescribing information]. Newton, MA: Karyopharm Therapeutics, Inc.; June 2020.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 June 27, 2020.
542. The NCCN B-Cell Lymphomas 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 July 10, 2020.

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

135. 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).

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
320. 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.

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.)

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
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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Zejula™ (niraparib capsules – Tesaro, Inc.)

DATE REVIEWED: 11/20/2019; selected revision 05/13/2020

OVERVIEW
Zejula, a poly (ADP-ribose) polymerase (PARP) inhibitor, is indicated[1]:
1) For the 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;
2) For the 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;
3) Zejula For the 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

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). 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 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

136. Ovarian, Fallopian Tube, or Primary Peritoneal Cancer –Maintenance Therapy. Approve for 3 years if the 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 and B):
A) The patient has tried at least three prior chemotherapy regimens.
Note: Examples of chemotherapy regimens are carboplatin/gemcitabine, carboplatin/liposomal doxorubicin, carboplatin/paclitaxel, cisplatin/gemcitabine, capecitabine, irinotecan; AND
B) The 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

Zejula 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.)

73. 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. Zejula™ capsules [prescribing information]. Waltham, MA: Tesaro, Inc.; April 2020.
379. 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 May 11, 2020.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Zelboraf® (vemurafenib tablets – Genentech/Daiichi Sankyo)

REVIEW DATE: 06/18/2019

OVERVIEW

Zelboraf, a BRAF inhibitor, is indicated for the following indications:
1. Erdheim-Chester disease, for treatment of patients with the *BRAF V600* mutation; AND
2. Melanoma, for treatment of unresectable or metastatic disease with *BRAF V600E* mutation as detected by a Food and Drug Administration (FDA)-approved test (Note that Cotellic® (cobimetinib tablets) is a MEK inhibitor that is indicated to be given in combination with Zelboraf in a similar patient population with melanoma);[1] AND

Zelboraf is not recommended for use in patients with wild-type BRAF melanoma.

Disease Overview

Mutations in the BRAF gene are common in several types of cancer.[2] The BRAF protein is normally switched on and off in response to signals that control cell growth and development; however, mutations cause the BRAF protein to be continuously active. This over activity may contribute to the growth of

cancers by allowing abnormal cells to grow and divide uncontrollably. The V600E mutation is the most common *BRAF* gene mutation identified in cancers, particularly in melanoma.

ECD is a rare non-Langerhans histiocytosis. There is a *BRAF V600* mutation estimated in between 38% and 100% of patients with ECD.[8] Although multiple systems may be affected, clinical findings most often exhibit in the CNS or as bone pain.

Guidelines

Prior to approval of Zelboraf guidelines for ECD (2014) list Zelboraf as a first- or second-line treatment option.[8] The National Comprehensive Cancer Network (NCCN) also supports use of Mekinst in multiple cancers.

FDA-Approved Indications

- Melanoma: Guidelines (version 2.2019 – March 12, 2019) recommend BRAF + MEK inhibitor combinations (e.g., Zelboraf + Cotellic, Tafinlar + Mekinist, Braftovi + Mektovi) for first-line (preferred if clinically needed for early response) and subsequent treatment of metastatic or unresectable melanoma with a V600 activating mutation.[3] While combination BRAF/MEK inhibition is preferred, NCCN notes that if contraindicated, monotherapy with a BRAF inhibitor (Tafinlar or Zelboraf) are recommended options, particularly for patients who are not appropriate candidates for checkpoint immunotherapy. Tafinlar + Mekinist is also recommended in guidelines as adjuvant therapy (including for nodal recurrance) in some patients with Stage III disease, including use post-surgery or use after complete lymph node dissection.

Other Uses With Supportive Evidence

- Colon Cancer: NCCN guidelines for colon cancer (version 2.2019 – May 15, 2019) recommend BRAF/MEK inhibitor combinations for *BRAF V600E*-mutated disease.[4] For primary treatment (following adjuvant chemotherapy) or as subsequent use, Zelboraf + ironotecan + Erbitux (cetuximab IV infusion) or Vectibix (panitumumab IV infusion) is a recommended treatment option. Subsequent use of either Braftovi + Mektovi or Tafinlar + Mekinist are also treatment options recommended in combination with Erbiux or Vectibix.
- Hairy Cell Leukemia: NCCN guidelines for hairy cell leukemia (version 3.2019 – January 31, 2019) state that a purine analog (e.g., cladribine, Nipent) is recommended as initial therapy.[4] Zelboraf ± rituximab is listed as an option for patients with relapsed or refractory disease following one of these regimens.
- Non-Small Cell Lung Cancer: NCCN guidelines for NSCLC (version 4.2019 – April 29, 2019) list Tafinlar + Mekinist as a first-line therapy for tumors with a *BRAF* mutation.[5] NCCN also notes that monotherapy with a BRAF inhibitor (Tafinlar or Zelboraf) is a treatment option when combination therapy is not tolerated.
- Thyroid Cancer: NCCN guidelines for thyroid cancer (version 1.2019 – May 28, 2019) list Tafinlar and Zelboraf as treatment options for iodine-refractory differentiated thyroid cancer with a *BRAF V600E* mutation.[6] This recommendation is for follicular, Hürthle cell, and papillary cancer subtypes.

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 (ECD).** 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)** The patient has unresectable, advanced, or metastatic melanoma; AND
   - **B)** The patient has *BRAF V600* mutation-positive disease.

Other Uses with Supportive Evidence

9. **Colon or Rectal Cancer.** Approve for 3 years if the patient meets the following (A, B, and C):
   - **10.** The patient has *BRAF V600E* mutation-positive disease; AND
   - **11.** The patient has previously received a chemotherapy regimen for colon or rectal cancer.
     NOTE: This includes previous adjuvant use of chemotherapy. Examples of previous 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); AND

12. The agent is prescribed as part of a combination regimen for colon or rectal cancer. NOTE: examples of combination regimens include: Zelboraf/ironotecan/Erbitux (cetuximab IV infusion), Zelboraf/ironotecan/Vectibix (panitumumab IV infusion). .

10. Hairy Cell Leukemia. Approve for 3 years if the patient meets BOTH of the following conditions (A and B):
- **A)** The patient has relapsed/refractory hairy cell leukemia; AND
- **B)** The patient has tried at least one other therapy for hairy cell leukemia (e.g., cladribine, Nipent™ [pentostatin injection], rituximab injection, Intron® A [interferon alpha-2b injection]).

11. Non-Small Cell Lung Cancer (NSCLC). Approve for 3 years if the patient has *BRAF V600E* mutation-positive disease.

12. Thyroid Cancer, Differentiated. Approve Zelboraf for 3 years if the patient meets ALL of the following conditions (A, B, and C):
- **D)** The patient has differentiated thyroid carcinoma (i.e., papillary, follicular, or Hürthle cell); AND
- **E)** The patient has disease that is refractory to radioactive iodine therapy; AND
- **F)** The patient has *BRAF* mutation-positive disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Zelboraf 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.)

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

321. Zelboraf® tablet, oral [prescribing information]. South San Francisco, CA: Genentech USA, Inc.; November 2017.
322. Genetic Home Reference. BRAF gene. National Institutes of Health, US Department of Health & Human Service Web Site. Reviewed August 2018. Accessed on June 4, 2019. Available at: https://ghr.nlm.nih.gov/gene/BRAF.
323. The NCCN Melanoma Clinical Practice Guidelines in Oncology (Version 2.2019 – March 12, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 4, 2019.
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324. The NCCN Hairy Cell Leukemia Clinical Practice Guidelines in Oncology (Version 3.2019 – January 31, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 6, 2019.
325. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 4.2019 – April 29, 2019). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 6, 2019.
326. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (Version 1.2019 – May 28, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 6, 2019..
327. Brose MS, Cabanillas ME, Cohen EE, et al. Vemurafenib in patients with BRAF(V600E)-positive metastatic or unresectable papillary thyroid cancer refractory to radioactive iodine: a non-randomised, multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2016;17(9):1272-1282.
328. Diamond EL, Dagna L, Hyman DM, et al. Consensus guidelines for the diagnosis and clinical management of Erdheim-Chester disease. *Blood.* 2014;124(4):483-492.
329. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 2.2019 – May 15, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 13, 2019.

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

13. **Erdheim-Chester Disease.** Approve for 3 years if the patient has *BRAF V600* mutation-positive disease.

14. **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

15. **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).

16. **Non-Small Cell Lung Cancer.** Approve for 3 years if the patient has *BRAF V600E* mutation-positive disease.

17. **Thyroid Cancer, Differentiated.** Approve Zelboraf for 3 years if the patient meets ALL of the following conditions (A, B, and C):
    G) Patient has differentiated thyroid carcinoma; AND
    Note: Examples of differentiated thyroid carcinoma include papillary, follicular, or Hürthle cell thyroid cancers.
    H) Patient has disease that is refractory to radioactive iodine therapy; AND
    I) Patient has *BRAF* mutation-positive disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Zelboraf 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
330. Zelboraf® tablet, oral [prescribing information]. South San Francisco, CA: Genentech USA, Inc.; May 2020.
331. 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.
332. 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.
333. 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.
334. 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.

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

145. 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:

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
543. Zolinza® capsules [prescribing information]. Whitehouse Station, NJ: Merck & Co.; December 2018.
544. 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.
545. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Zydelig® (idelalisib tablets – Gilead)

DATE REVIEWED: 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 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.

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 3 years in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

137. 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).

138. 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).

139. 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

74. 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

335. Zydelig® tablets [prescribing information]. Foster City, CA: Gilead Sciences; October 2018.
336. Zydelig REMS program. Available at: http://www.zydeligrems.com/. Accessed on May 29, 2020.
337. 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.
338. 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. [and supplementary appendix]

339. 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.
340. Hallek M, Shanafelt TD, Eichhorst B. Chronic lymphocytic leukemia. *Lancet*. 2018;391:1524-1537.
341. 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. [and supplementary appendix]
342. 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.
343. 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.
344. 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	Date Reviewed
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.)

75. 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. Zykadia™ capsules and tablets [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals; March 2019.
346. 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.
347. 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.
348. 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.
349. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Adcetris® (brentuximab injection for intravenous use – Seattle Genetics, Inc.)

REVIEW DATE: 09/25/2019

OVERVIEW

Adcetris is a CD30-directed antibody, produced in Chinese hamster ovary cells, conjugated with monomethyl auristatin E (MMAE).[1] CD30 is expressed on systemic anaplastic large cell lymphoma cells and on Hodgkin Reed-Sternberg cells in classical Hodgkin lymphoma and MMAE is a microtubule-

disrupting agent. The anticancer activity is due to the binding of Adcetris to the CD30 receptor, followed by internalization and release of MMAE. MMAE then binds to tubulin disrupting the microtubule network leading to cell cycle arrest and apoptosis.

Adcetris is FDA-approved for the treatment of adults with:

- Previously untreated Stage III or IV classical Hodgkin lymphoma, in combination with doxorubicin, vinblastine, and dacarbazine.
- Classical Hodgkin lymphoma at high risk of relapse or progression as post-autologous hematopoietic stem cell transplantation consolidation.
- Classical Hodgkin lymphoma after failure of autologous hematopoietic stem cell transplantation or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not autologous hematopoietic stem cell transplantation candidates.
- Previously untreated 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 combination with cyclophosphamide, doxorubicin, and prednisone.
- Systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen.
- Primary cutaneous anaplastic large cell lymphoma or CD30-expressing mycosis fungoides who have received prior systemic therapy.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) Hodgkin Lymphoma Clinical Practice Guidelines (version 2.2019 – July 15, 2019) 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 2.2019 – December 17, 2018) 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, 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 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 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 2.2019 – December 17, 2018) 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 4.2019 – June 18,2019) 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 marginal zone lymphoma to CD30+ DLBCL, CD30+ DLBCL, CD30+ high-grade B-cell lymphoma, CD30+ 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

146. Hodgkin Lymphoma. 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 classical Hodgkin lymphoma; AND
- **C)** Adcetris is prescribed by or in consultation with an oncologist.

147. T-Cell Lymphoma. 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)** Adcetris is used for CD30+ T-cell lymphoma.
  (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+ cutaneous anaplastic large cell lymphoma, CD30+ lymphomatoid papulosis, CD30+ breast implant-associated anaplastic large cell lymphoma, CD30+ T-cell leukemia/lymphoma);[1,2,4] AND
- **C)** Adcetris is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

148. B-Cell Lymphoma. 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)** Adcetris is used as second-line or subsequent therapy for CD30+ B-cell lymphoma. (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);[2,6] AND
- **C)** Adcetris is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Adcetris 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.

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

546. Adcetris® injection [prescribing information]. Bothell, WA: Seattle Genetics, Inc.; November 2018.
547. The NCCN Drugs and Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 16, 2019. Search term: brentuximab.
548. The NCCN Hodgkin Lymphoma Clinical Practice Guidelines in Oncology (Version 2.2019 – July 15, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 16, 2019.
549. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 2.2019 – December 17, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 16, 2019.
550. The NCCN Primary Cutaneous Lymphomas Clinical Practice Guidelines in Oncology (Version 2.2019 – December 17, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 16, 2019.
551. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 4.2019 – June 18, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 16, 2019.

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

149. 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

150. 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:

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

552. Aliqopa™ injection for intravenous use [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; February 2020.
553. 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.

554. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Arsenic Trioxide injection for intravenous use (Trisenox® – Teva Pharmaceuticals, generics)

REVIEW DATE: 09/25/2019

OVERVIEW

The mechanism of action of arsenic trioxide has not been entirely elucidated, however it has been demonstrated *in vitro* that it causes morphologic changes and DNA fragmentation characteristic of apoptosis in NB4 human promyelocytic leukemia cells.[1] In addition, arsenic trioxide has been shown to damage or degrade the fusion protein promyelocytic leukemia (PML)-retinoic acid receptor (RAR)-alpha.

Arsenic trioxide is indicated:

- In combination with tretinoin for the treatment of adults with newly-diagnosed low-risk acute promyelocytic leukemia (APL) 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 2.2020 – September 3, 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 2.2019 – December 17, 2018) 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

151. Acute Promyelocytic Leukemia. Approve for 1 year if arsenic trioxide is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

152. 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) The patient has acute or lymphoma subtype; AND
C) Patient has tried chemotherapy.
(Note: Examples include CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone], CHOEP [cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone]); AND
D) Arsenic trioxide will be used in combination with interferon alfa-2b.
(Note: Includes Intron A); AND
E) Arsenic trioxide is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Arsenic trioxide 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.

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

555. Trisenox® injection for intravenous use [prescribing information]. North Wales, PA: Teva Pharmaceuticals; June 2019.
556. The NCCN Drugs and Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 3, 2019. Search term: arsenic trioxide.
557. 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 September 3, 2019.
558. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 2.2019 – December 17, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://nccn.org. Accessed on September 3, 2019.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Arzerra® (ofatumumab injection for intravenous use – Novartis)

REVIEW DATE: 10/09/2019

OVERVIEW

Arzerra is a human IgG1 monoclonal antibody that binds to the large and small extracellular loops of the CD20 molecule.[1] The Fab domain of the antibody binds to the CD20 molecule while the Fc domain mediates immune effector function which result in B-cell lysis. Potential mechanisms of cell lysis include complement-mediated cytotoxicity and antibody-dependent, cell-mediated cytotoxicity.

Arzerra is indicated:

- In combination with chlorambucil, for the treatment of previously untreated patients with chronic lymphocytic leukemia (CLL) for whom fludarabine-based therapy is considered inappropriate;
- In combination with fludarabine and cyclophosphamide for the treatment of relapsed CLL;
- For extended treatment of patients who are in complete or partial response after at least two lines of therapy for recurrent or progressive CLL;
- For the treatment of patients with CLL refractory to fludarabine and alemtuzumab.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (version 1.2020 – August 23, 2019) 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 Macroglobulinema/Lymphoplasmacytic Lymphoma (version 2.2019 – September 14, 2018) recommends Arzerra as a single agent or in combination therapy in rituximab (Rituxan, Truxima) intolerant patients for previously treated disease that does not response to primary treatment or for relapsed or progressive disease.[2,4]

The NCCN guidelines on B-Cell Lymphomas (version 4.2019 – June 18, 2019) recommends Arzerra as a substitute for rituximab products 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]

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

153. 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)** Arzerra is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

154. 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) The patient is intolerant to a rituximab product; AND
C) The patient has relapsed or progressive disease; AND
D) Arzerra is prescribed by or in consultation with an oncologist.

155. 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) The patient experienced an adverse event or intolerance to a rituximab product or Gazyva® (obinutuzumab injection).
(NOTE: Examples of adverse events or intolerance include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, toxic epidermal necrolysis]; AND
C) Arzerra is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Arzerra 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.

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

559. Arzerra® [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; August 2016.
560. The NCCN Drugs and Biologics Compendium. © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on November 27, 2018. Search term: ofatumumab.
561. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma 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 August 27, 2019.
562. The NCCN Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma Clinical Practice Guidelines in Oncology (Version 2.2019). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 27, 2019.
563. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 4.2019 – June 18, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 27, 2019.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Asparlas™ (calaspargase pegol mknl injection, for intravenous use)

DATE REVIEWED: 12/11/2019

OVERVIEW

Asparlas is a conjugate of L-asparaginase, produced by *E. coli*, and monomethoxypolyethylene glycol (mPEG) with a succinimidyl carbonate (SC) linker.[1] The SC 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.

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]

Guidelines

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for ALL (version 2.2019 – May 15, 2019) and Pediatric ALL (version 2.2020 – November 25, 2019) 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 1 year in duration as 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

13. Acute Lymphoblastic Leukemia. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** The patient is aged 1 month to 21 years; AND
- **B)** Asparlas is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Asparlas 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.

145. 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. Asparlas™ [prescribing information]. Boston, MA: Servier Pharmaceuticals LLC; September 2019.
565. The NCCN Drugs & Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 3, 2019. Search term: calaspargase.
566. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (Version 2.2019 – May 15, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 3, 2019.
567. 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 December 3, 2019.

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

28. 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.

29. 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:

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

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.

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:

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

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.

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:

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
568. Beleodaq® injection for intravenous use [prescribing information]. Irvine, CA: Spectrum Pharmaceuticals, Inc.; January 2020.
569. 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.
570. 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.
571. 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.

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

14. **B-Cell Non-Hodgkin Lymphoma.** Approve for 6 months if bendamustine is prescribed by or in consultation with an oncologist.

15. **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

16. **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.

17. **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.

18. **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.

19. **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:

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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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:

148. 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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PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Bevacizumab Products

- Avastin® (bevacizumab injection for intravenous injection – Genentech, Inc.)
- Mvasi™ (bevacizumab-awwb injection for intravenous infusion – Amgen)
- Zirabev™ (bevacizumab-bvzr injection for intravenous infusion – Pfizer)

DATE REVIEWED: 04/01/2020; 06/10/2020 selected revision

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:

1) cervical cancer (persistent, recurrent, or metastatic), in combination with paclitaxel and cisplatin OR paclitaxel and topotecan;
2) metastatic colorectal cancer (mCRC), 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;
3) treatment of recurrent glioblastoma in adults;
4) non-squamous non-small cell lung cancer (NSCLC), in combination with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent or metastatic disease;
5) recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer 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 Avastin 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;
6) metastatic renal cell carcinoma (mRCC) in combination with interferon alfa subcutaneous injection;
7) 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.

Bevacizumab is available as a solution and is supplied in 100 mg and 400 mg preservative-free, single-use vials that deliver 4 mL and 16 mL of bevacizumab (25 mg/mL), respectively.[1] The dose of bevacizumab is diluted in a total volume of 100 mL of 0.9% sodium chloride injection. The first dose is given as an intravenous infusion over 90 minutes. The second dose is infused over 60 minutes if the first dose was tolerated, and the third and all subsequent doses are given over 30 minutes, if the 60 minute infusion was tolerated.

Guidelines

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines on **cervical cancer** (version 3.2019 – December 17, 2018) recommend bevacizumab for treatment of local/regional recurrence or Stage IVB or distant metastases in patients with cervical cancer (squamous cell carcinoma or adenocarcinoma) as first-line preferred combination regimen with paclitaxel and cisplatin (category 1), or with carboplatin and paclitaxel (category 2A), or with topotecan and paclitaxel (category 1).[2] It is also recommended for second-line, single-agent therapy (category 2B).

The NCCN clinical practice guidelines on **colon cancer** (version 2.2020 – March 3, 2020) recommendations for bevacizumab treatment are as follows:[3,4]

- In combination with capecitabine or with FOLFOX, FOLFIRI, CapeOX, FOLFOXIRI, OR 5-FU/LV as one of the following (category 2A):
  - As primary treatment for advanced or metastatic disease;
  - For unresectable synchronous metastases to liver and/or lung and other sites;
  - As primary treatment for synchronous abdominal/peritoneal metastases that are non-obstructing, or following local therapy for patients with imminent or existing obstruction;
  - As primary treatment for unresectable metachronous metastases in combination with FOLFIRI or irinotecan.;
- Primary treatment for unresectable synchronous liver and/or lung metastases in combination with one of the following: FOLFOX, FOLFIRI, FOLFOXIRI, or CapeOX (category 2A);
- The preferred anti-angiogenic therapy* as primary treatment for patients with unresectable metachronous metastases and previous adjuvant FOLFOX or CapeOX within the past 12 months in combination with irinotecan or FOLFIRI (category 2A);
- As subsequent therapy for advanced or metastatic disease (category 2A):
  - As the preferred anti-angiogenic agent* in combination with irinotecan or FOLFIRI in patients previously receiving oxaliplatin-based therapy without irinotecan;
  - In combination with FOLFOX or CapeOX in patients previously receiving irinotecan-based therapy without oxaliplatin;
  - As the preferred anti-angiogenic agent* in combination with irinotecan or FOLFIRI for patients previously treated with fluoropyrimidine therapy without irinotecan or oxaliplatin; or in combination with FOLFOX or CAPEOX in this population; or irinotecan + oxaliplatin.

The NCCN clinical practice guidelines on **rectal cancer** (version 2.2020 – March 3, 2020) recommendations for bevacizumab treatment are as follows:[4,5]

- In combination with capecitabine or with a FOLFOX, FOLFIRI, FOLFOXIRI, CapeOX or 5-FU/LV regimen for one of the following (All of these are category 2A except adjuvant therapy which is 2B.):
  - Primary therapy for T3, N0, any T, N1-2, or T4 and/or locally unresectable or medically inoperable disease if resection is contraindicated after neoadjuvant therapy;
  - Primary therapy for unresectable synchronous metastases or for medically inoperable disease;
  - After primary treatment with chemoradiation or local therapy for symptomatic unresectable synchronous metastases or medically inoperable disease;
  - Adjuvant therapy after resection and/or local therapy of resectable metachronous metastases for patients who received previous chemotherapy or had growth on neoadjuvant chemotherapy;
  - Primary treatment for unresectable metachronous metastases in patients who have not received previous adjuvant FOLFOX or CapeOX within the past 12 months;

  - Adjuvant therapy for unresectable metachronous metastases that converted to resectable disease after primary treatment;
  - For unresectable metachronous metastases that remain unresectable after primary treatment;
- As the preferred anti-angiogenic therapy* as primary treatment, in combination with irinotecan or FOLFIRI in patients with unresectable metachronous metastases and previous adjuvant FOLFOX or CapeOX within the past 12 months (category 2A);
- As subsequent therapy after first progression of unresectable advanced or metastatic disease in combination with chemotherapy (category 2A).

The NCCN clinical practice guidelines on **central nervous system (CNS) cancers** (version 1.2020 – March 10, 2020) recommend bevacizumab as a preferred single-agent therapy for recurrent anaplastic gliomas (category 2A).[6] Anaplastic gliomas includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (A), and other rare anaplastic gliomas. Bevacizumab is also recommended as a preferred single-agent therapy for glioblastoma (category 2A) and in combination with chemotherapy (carmustine or lomustine, TMZ, carboplatin) [category 2B]. The NCCN guidelines recommend that bevacizumab be considered as a single-agent treatment for recurrence therapy in adults with *intracranial and spinal ependymoma* (excluding subependymoma) [category 2A]. It is also recommended for meningiomas either as monotherapy (category 2A) or in combination with Afinitor (everolimus tablets) [category 2B]. Patients with good performance status who have evidence of radiographic progression may benefit from continuing bevacizumab alone to prevent rapid neurologic deterioration. In patients with glioblastoma or anaplastic gliomas, Bevacizumab plus chemotherapy can be considered in patients who have failed bevacizumab monotherapy.

The NCCN clinical practice guidelines on **NSCLC** (version 3.2020 – February 11, 2020)[4,7] recommend bevacizumab therapy in combination with carboplatin and paclitaxel (category 1), carboplatin and Alimta (category 2A), cisplatin and Alimta (category 2A) for recurrence or metastases in patients with performance status 0 to 1 for tumors of non-squamous cell histology (i.e., adenocarcinoma (with mixed subtypes), large cell carcinoma) and no history of recent hemoptysis for the following uses:

1) initial systemic therapy if *EGFR*, *ALK*, *ROS1*, *BRAF* negative or unknown, and PD-L1 < 50 or unknown;
2) first-line or subsequent therapy for *BRAF V600E*-mutation positive tumors;
3) subsequent therapy for sensitizing *EGFR* mutation-positive tumors after prior targeted therapy (e.g., Tarceva® [erlotinib tablets], Tagrisso® [osimertinib tablets]);
4) subsequent therapy for *ALK* rearrangement-positive tumors after previous targeted therapy (e.g., Xalkori® [crizotinib capsules], Alecensa® [alectinib capsule]);
5) subsequent therapy for *ROS1* rearrangement-positive tumors and prior Xalkori or Zykadia therapy;
6) First-line or subsequent therapy for PD-L1 expression-positive (≥ 50%) tumors and.

Bevacizumab is also recommended in the NCCN guidelines as *continuation maintenance* therapy if given first line with chemotherapy for recurrence or metastasis.[7] This is in patients who achieve tumor response or stable disease following initial cytotoxic therapy.

The NCCN clinical practice guidelines on **ovarian cancer** including fallopian tube or primary peritoneal cancer (version 1.2020 – March 11, 2020) recommendations for bevacizumab treatment of ***epithelial*** ovarian cancer/fallopian tube cancer/primary peritoneal cancer are as follows:[8]

- Therapy for persistent disease or recurrence for one of the following (category 2A):
  - As preferred therapy if *platinum-sensitive*, in combination with chemotherapy.
  - As preferred therapy if *platinum-resistant*, in combination with chemotherapy; or
  - As preferred targeted therapy as a single agent for both platinum-sensitive and platinum-resistant disease.
- Maintenance therapy for *platinum-sensitive* persistent disease or recurrence following response.

- Consider as neoadjuvant chemotherapy in combination with paclitaxel and carboplatin for bulky Stage II to IV disease or poor surgical candidates (category 2A). Bevacizumab can also be used with this combination (paclitaxel and carboplatin) for primary adjuvant treatment in stage I to IV disease.
- Bevacizumab is also recommended (mostly in combination with chemotherapy, but sometimes as single agent) for treatment of Other Less Common Histopathologies such as carcinosarcoma, clear-cell carcinoma, mucinous carcinoma, serous/endometrioid epithelial carcinoma, and malignant sex cord stromal tumors either either for adjuvant therapy or for treatment of systemic disease.

For **kidney cancer**, bevacizumab's efficacy was established using Roferon®-A (interferon alfa-2a injection)[9] which is no longer available. Subsequently, bevacizumab was studied in combination with Intron A.[10] The NCCN clinical practice guidelines on **kidney cancer**[11] (version 2.2020 – August 5, 2019) recommend bevacizumab as therapy for relapse or Stage IV disease as follows: 1) in combination with interferon alfa-2 (Roferon A, Intron A) in favorable risk and poor/intermediate risk patients as first-line therapy for disease with predominant clear cell histology (category 1). This combination is listed as agents useful under certain circumstances; 2) as a single-agent subsequent therapy for predominant clear cell histology as "useful under certain circumstances" (category 2B); 3) as single-agent systemic therapy for non-clear cell histology, useful under certain circumstances (category 2A); and 4) in combination with erlotinib (for selected patients with advanced papillary renal cell carcinoma including hereditary leiomyomatosis and renal cell cancer) or everolimus/Afinitor® Disperz™ (everolimus tablets for oral suspension) (category 2A).

The NCCN clinical practice guidelines on **breast cancer** (version 3.2020 – March 6, 2020) recommend bevacizumab in combination with paclitaxel as "useful in certain circumstances" for recurrent or metastatic (stage IV) HER2-negative disease and endocrine therapy refractory (category 2A).[12] The guidelines note that sequential single agents are preferred options, but chemotherapy cmbinations may be used in select patients with high tumor burden, rapidly progressing disease, and visceral crisis. Regarding bevacizumab, the guidelines state that randomized trials in metastatic breast cancer document that adding bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival or quality of life. The time to progression impact may vary among cytotoxic agents used with bevacizumab and appears greatest with bevacizumab in combination with weekly paclitaxel.

The NCCN clinical practice guidelines on **malignant pleural mesothelioma** (version 1.2020 – November 27, 2019) recommend bevacizumab in combination with cisplatin and Alimta (category 1) or with carboplatin and Alimta (category 2A) followed by single-agent maintenance bevacizumab as treatment for 1) unresectable clinical Stage I to III disease and tumors of epithelial histology, or 2) clinical Stage IV disease, tumors of sarcomatoid or mixed histology, or medically inoperable tumors in patients with performance status 0 to 2.[13] The NCCN guidelines recommend intravenous bevacizumab 15 mg per kg on Day 1 given every 3 weeks for 6 cycles in combination with Alimta with cisplatin or carboplatin for first-line combination therapy. This combination therapy may be followed by maintenance bevacizumab 15 mg per kg given every 3 weeks until disease progression.

The NCCN Compendium for bevacizumab recommends its use in endometrial carcinoma as a single agent or in combination with other chemotherapy upon progression on prior chemotherapy (category 2A).[4] It is also recommended for small bowel adenocarcinoma in combination with other chemotherapy for initial therapy (category 2A). For soft tissue sarcoma, bevacizumab is recommended for use in combination with temozolomide for the treatment of solitary fibrous tumor and hemangiopericytoma. It is also recommended as single agent therapy for angiosarcoma (category 2A for both).

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 (AEs) 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 is recommended in those who meet one of the following criteria:

FDA-Approved Indications

25. 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)** The patient has recurrent or metastatic cervical cancer.

26. Colon or Rectal Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Bevacizumab is prescribed by or in consultation with an oncologist; AND
- **B)** The patient has advanced or metastatic colon or rectal cancer [Stage IV]; AND
- **C)** Bevacizumab is used in combination with a chemotherapy regimen.
  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; AND
- **D)** Bevacizumab is not being used for adjuvant treatment of colon cancer.

27. Central Nervous System Tumors – Glioblastoma (glioblastoma multiforme [GBM], Grade IV astrocytoma), Anaplastic Gliomas, Meningiomas, Intracranial and Spinal Ependymoma (Excludes Subependymoma) in Adults. 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 patient has tried at least one other therapy.
  Note: Examples of other therapies are temozolomide capsules or injection, radiotherapy.

28. 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)** The patient has not received prior systemic therapy.

29. Non-Small Cell Lung Cancer (NSCLC). Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** Bevacizumab is prescribed by or in consultation with an oncologist; AND
- **B)** The 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 for first-line treatment; OR
  - **ii.** If the NSCLC tumor is positive for any one of the targetable mutations (i.e., epidermal growth factor receptor (*EGFR*) mutations, anaplastic lymphoma kinase (*ALK*) fusions, ROS proto-oncogene 1 [*ROS1*]) at least one of the targeted therapy agents has been tried and bevacizumab is used as subsequent therapy; OR
  - **iii.** If the NSCLC tumor is *BRAF V600E* mutation-positive, bevacizumab is used as either first-line or subsequent therapy; OR
  - **iv.** The NSCLC tumor is negative or unknown for targetable mutations (e.g., *EGFR, ALK, ROS1, BRAF*) and the patient meets ONE of the following criteria (a or b):
    - **a)** Bevacizumab is used as initial therapy in combination with platinum chemotherapy (cisplatin or carboplatin); OR
    - **b)** Bevacizumab is used as subsequent therapy and is 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)** The 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)** Bevacizumab is prescribed by or in consultation with an oncologist; AND
- **B)** The patient has recurrent or metastatic human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
- **C)** Bevacizumab 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)** The patient has progressed on prior chemotherapy.
  Note: Examples of chemotherapy are carboplatin, cisplatin, paclitaxel, docetaxel, doxorubicin.

10. 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).

11. 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)** The 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.
    Note: Examples of chemotherapy regimens are Alimta [pemetrexed injection], cisplatin, carboplatin; OR
  - **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.

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 – Angiosarcoma and Solitary Fibrous Tumor/Hemangiopericytoma. Approve for 1 year if 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 (Aand 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

Bevacizumab 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. 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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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):
- **20.** Patient is ≥ 18 years of age; AND
- **21.** Patient has tried at least four prior systemic lines of therapy; AND
- **22.** 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).
- **23.** 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:

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

587. Blenrep™ intravenous infusion [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; August 2020.
588. 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.

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) ≥ 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

156. 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:

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

589. Blincyto® injection for intravenous use [prescribing information]. Thousand Oaks, CA: Amgen; March 2020.
590. 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.
591. 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.
592. 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: blinatumomab.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Carmustine Injection (BICNU® – Heritage Pharmaceuticals, generics)

DATE REVIEWED: 12/18/2019

OVERVIEW

Carmustine injection, a nitrosourea, is approved for the following uses as a palliative agent as a single agent or in established combination therapy in the following conditions:[1]

- Brain tumors, including glioblastoma, brainstem glioma, medulloblastoma, astrocytoma, ependymoma, and metastatic brain tumors; AND
- Multiple myeloma, in combination with prednisone; AND
- Hodgkin's lymphoma, in relapsed or refractory disease in combination with other approved drugs; AND
- Non-Hodgkin's lymphoma, in relapsed or refractory disease in combination with other approved drugs.

Guidelines

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines on Central Nervous System Cancers (version 3.2019 – October 18, 2019) supports use of carmustine injection for certain adults with recurrent or progressive low-grade glioma/pilocytic and infiltrative supratentorial astrocytoma/oligodendroglioma, recurrent treatment of anaplastic glioma, glioblastoma, adult intracranial and spinal ependymoma (excluding subependymoma).[2,3] Carmustine injection is also part of a Preferred regimen (in combination with thiotepa) as consolidation therapy with stem cell rescue in patients with primary CNS lymphoma.[2,4]

The NCCN clinical practice guidelines on Hodgkin Lymphoma (version 2.2019 – July 15, 2019) recommend carmustine as part of a chemotherapy regimen (e.g., MiniBEAM [carmustine/cytarabine/etoposide/melphalan] for relapsed or refractory disease.[5]

The NCCN clinical practice guidelines on Multiple Myeloma (version 2.2020 – October 9, 2019) and B-Cell Lymphomas (version 5.2019 – September 23, 2019) do not provide recommendations on the use of carmustine for the treatment of multiple myeloma or non-Hodgkin's lymphoma.[6,7]

POLICY STATEMENT

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

Because of the specialized skills required for evaluation and diagnosis of patients treated with carmustine products as well as the monitoring required for adverse events and long-term efficacy, approval requires carmustine 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 carmustine products is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Central Nervous System Tumor** (Note: Includes Adult Low-Grade Infiltrative Supratentorial Astrocytoma/Oligodendroglioma, Anaplastic Gliomas, Glioblastoma, Adult Intracranial and Spinal Ependymoma, Primary Central Nervous System Lymphoma). 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.** The patient has recurrent or progressive disease; OR
     - **ii.** The agent is being used in a regimen with stem cell rescue.
       Note: For example, as consolidation therapy in combination with thiotepa with stem cell rescue; AND
   - **B)** The agent is prescribed by or in consultation with an oncologist.

2. **Hodgkin Lymphoma.** 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 relapsed or refractory disease; AND
   - **C)** The agent is being used as part of a chemotherapy regimen.
     Note: For example, as a component of MiniBEAM (carmustine/cytarabine/etoposide/melphalan); AND
   - **D)** The agent is prescribed by or in consultation with an oncologist.

3. **Non-Hodgkin's Lymphoma.** 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)** The agent is being used as part of a chemotherapy regimen; AND
   - **C)** The agent is prescribed by or in consultation with an oncologist.

4. **Multiple Myeloma.** Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** The agent is being used with prednisone: AND
   - **B)** The agent is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Carmustine 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
593. BICNU [prescribing information]. East Brunswick, NJ: Heritage Pharmaceuticals; September 2018.
594. The NCCN Central Nervous System Clinical Practice Guidelines in Oncology (Version 3.2019 – October 18, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 21, 2019.
595. The NCCN Drugs and Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 21, 2019. Search term: carmustine.
596. The NCCN Drugs and Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 21, 2019. Search term: carmustine implant.
597. The NCCN Hodgkin Lymphoma Clinical Practice Guidelines in Oncology (Version 2.2019 – July 15, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 21, 2019.
598. 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 October 21, 2019.
599. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 5.2019 – September 23, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on October 21, 2019.

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

6. **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]).

7. **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.

8. **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).

9. 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.

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

380. Cyramza® injection for intravenous use [prescribing information]. Indianapolis, IN: Eli Lilly and Company; June 2020.
381. 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.
382. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (Version 4.2020 – May 21, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 3, 2020.
383. The NCCN Drugs & Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 3, 2020. Search term: ramucirumab.
384. The NCCN Gastric Cancer 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 3, 2020.
385. 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 3, 2020.
386. 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.
387. 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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- Park K, Kim JH, Cho EK, et al. East Asian subgroup analysis of a randomized, double-blind, phase 3 study of docetaxel and ramucirumab versus docetaxel and placebo in the treatment of stage IV non-small cell lung cancer following disease progression after one prior platinum-based therapy (REVEL). *Cancer Res Treat*. 2016;48(4):1177-1186.
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PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Darzalex Faspro Prior Authorization Policy

- Darzalex™ Faspro (daratumumab and hyaluronidase-fihj injection for subcutaneous use – Janssen Biotech, Inc.) Prior Authorization Policy

REVIEW DATE: 05/06/2020

OVERVIEW

Darzalex Faspro approved in 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; AND
- in newly diagnosed patients, in combination with Velcade (bortezumab injection), melphalan, and prednisone in those ineligible 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.

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 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

The National Comprehensive Cancer Network (NCCN) guidelines for multiple myeloma (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, are Darzalex IV/Pomalyst/dexamethasone are listed as other recommended regimens.

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. 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. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

10. Multiple Myeloma. Approve for 1 year if the patient meets BOTH of the following (A and B):
- **24.** 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)** The 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
- **25.** Darzalex Faspro is prescribed by or in consultation with an oncologist or a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Darzalex Faspro 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.

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

15. Darzalex Faspro [prescribing information]. Horsham, PA: Janssen Biotech, Inc.; May 2020.
16. 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.
17. 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	--	05/06/2020
Update	06/16/2020: Update overview to include updated NCCN guidelines. No criteria changes.	NA

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Darzalex™ (daratumumab injection for intravenous use – Janssen Biotech, Inc.)

DATE REVIEWED: 02/26/2020

OVERVIEW

Darzalex is a CD38-directed cytolytic antibody.[1] It binds to CD38 and inhibits the growth of CD38-expressing tumor myeloma cells. It is approved adults with multiple myeloma who meet the following:

- 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 two prior therapies (including Revlimid and a proteasome inhibitor), in combination with Pomalyst (pomalidomide capsules) 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.

Safety and efficacy is not established in patients < 18 years of age.

Guidelines

The NCCN Multiple Myeloma clinical practice guidelines (version 2.2020 – October 9, 2020) recommend Darzalex in treatment regimens for primary therapy.[2-3] Darzalex/Velcade/Thalomid/dexamethasone is recommended as primary therapy for transplant candidates. For patients who are non-transplant candidates, Darzalex/Revlimid/prednisone is a Preferred regimen, and Darxalex/Velcade/melphalen/prednisone is an Other regimen for primary treatment. For previously treated multiple myeloma, Darzalex/dexamethasone plus Velcade or Revlimid are among the Preferred regimens, whereas Darzalex monotherapy and Darzalex/ dexamethasone plus Kyprolis (carfilzomib injection) or Pomalyst are listed as other recommended regimens. The NCCN systemic light chain amyloidosis guidelines (version 1.2020 – December 6, 2019) list Darzalex as a therapy for previously treated disease.[4]

POLICY STATEMENT

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

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

11. Multiple Myeloma. Approve for 1 year if the patient meets BOTH of the following (A and B):
- **26.** The patient meets ONE of the following (i or ii):
  - **A)** Darzalex is used in combination with at least one other agent.
    Note: Examples of agents that may be used in combination with Darzalex includeRevlimid (lenalidomide capsules), Pomalyst (pomalidomide capsules), Thalomid (thalidomide capsules), melphalen, Velcade (bortezumab injection), or Kyprolis (carfilzomib injection); OR
  - **B)** The 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
- **27.** Darzalex is prescribed by or in consultation with an oncologist or a hematologist.

Other Uses with Supportive Evidence

12. Systemic Light Chain Amyloidosis. Approve for 1 year if the patient meets BOTH of the following (A and B):
- **A)** The patient has received 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; AND
- **B)** The agent is prescribed by or in consultation with an oncologist or a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Darzalex 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.

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

18. Darzalex [prescribing information]. Horsham, PA: Janssen Biotech, Inc.; September 2019.
19. 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: daratumumab.
20. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (Version 2.2020 – October 9, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 17, 2020.
21. The NCCN Systemic Light Chain Amyloidosis Clinical Practice Guidelines in Oncology (Version 1.2020 – December 6, 2019). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 17, 2020.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Decitabine injection for intravenous use (Dacogen® – Otsuka America Pharmaceutical, generics)

REVIEW DATE: 10/16/2019

OVERVIEW

Decitabine (Dacogen), a hypomethylating agent, is indicated for the treatment of adults with myelodysplastic syndromes (MDS) 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 Myelodysplastic Syndromes (Version 1.2020 – August 27, 2019) 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 Acute Myeloid Leukemia (Version 2.2020 – September 3, 2019) 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 Myeloproliferative Neoplasms (Version 3.2019 – September 4, 2019) 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

157. 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) The patient is ≥ 18 years of age; AND

B) Decitabine is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

158. Acute Myeloid Leukemia. Approve for 1 year 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 ≥ 60 years of age; OR
  - **ii.** The patient has relapsed or refractory disease; AND
- **B)** Decitabine is prescribed by or in consultation with an oncologist.

159. Blastic Plasmacytoid Dendritic Cell Neoplasm. 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)** Decitabine is used in combination with Venclexta® (venetoclax tablet); AND
- **C)** Decitabine is prescribed by or in consultation with an oncologist.

160. Myelofibrosis. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** The patient has accelerate phase, or blast/acute myeloid leukemia phase; AND
- **B)** Decitabine is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Decitabine 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.

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

600. Dacogen® injection for intravenous use [prescribing information]. Rockville, MD: Otsuka America Pharmaceutical; December 2018.
601. The NCCN Drugs and Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 10, 2019. Search term: decitabine.
602. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (Version 1.2020 – August 27, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 10, 2019.
603. 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 September 11, 2019.
604. 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 September 11, 2019.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Elzonris™ (tagraxofusp-erzs injection for intravenous use – Stemline Therapeutics)

DATE REVIEWED: 12/11/2019

OVERVIEW

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.

Elzonris is indicated for the treatment of blastic plasmacytoid dendritic cell neoplasm in adults and pediatric patients ≥ 2 years of age.[1]

Guidelines

The National Comprehensive Cancer Network clinical practice guidelines for Acute Myeloid Leukemia (Version 2.2020 – September 3, 2019) 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

161. Blastic Plasmacytoid Dendritic Cell Neoplasm. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** The patient is ≥ 2 years of age; AND
- **B)** Elzonris is prescribed by or consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Elzonris 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.

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

605. Elzonris™ [prescribing information]. New York, NY: Stemline Therapeutics; December 2018.
606. The NCCN Drugs & Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 3, 2019. Search term: tagraxofusp.
607. 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 December 3, 2019.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Empliciti™ (elotuzumab injection for intravenous use – Bristol-Myers Squibb)

DATE REVIEWED: 02/26/2020

OVERVIEW

Empliciti is a SLAMF7 (signaling lymphocytic activation molecule family member 7)-directed immunostimulatory antibody.[1] It attaches to SLAMF7 on myeloma cells and Natural Killer (NK) cells; therefore, it acts directly on myeloma cells plus enhances the activity of NK cells to kill the myeloma cells. In multiple myeloma, Empliciti is indicated for the following uses:

1. in patients with who have received one to three prior therapies, in combination with Revlimid (lenalidomide capsules) and dexamethasone; AND
2. in patients who have received at least two prior therapies (including Revlimid and a proteasome inhibitor), in combination with Pomalyst® (pomalidomide) and dexamethasone, .

If the dose of one drug in the regimen is delayed, interrupted, or discontinued, the treatment with the other drugs may continue as scheduled. However, if dexamethasone is delayed or discontinued, base the decision whether to administer Empliciti on clinical judgment (i.e., risk of hypersensitivity). Safety and efficacy have not been established in patients < 18 years of age.

Guidelines

The NCCN Multiple Myeloma clinical practice guidelines (version 2.2020 – October 9, 2019) recommend Empliciti in treatment regimens for patients who were previously treated for multiple myeloma.[3] In this population, Empliciti/Revlimid/dexamethasone is among the Preferred regimens, whereas Empliciti/Velcade (bortezomib injection)/dexamethasone and Empliciti/Pomalyst/dexamethasone are listed 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 Emplicti is recommended in those who meet the following criteria:

FDA-Approved Indications

13. Multiple Myeloma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):

28. The patient has tried at least one other regimen for multiple myeloma.
Note: Examples of agents used in other regimens include Velcade (bortezumab injection), Revlimid (lenalidomide capsules), cyclophosphamide, Darzalex (daratumumab injection); AND

29. Empliciti is used in combination with at least one other agent.
Note: Examples of agents that may be used in combination with Empliciti include Revlimid® (lenalidomide capsules), Velcade (bortezomib injection), and Pomalyst (pomalidomide capsules); AND

30. Empliciti is prescribed by or in consultation with an oncologist or a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Empliciti 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.

157. 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. Empliciti® [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; October 19, 2019.
23. 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: elotuzumab.
24. 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 February 17, 2020.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Enhertu® (fam-trastuzumab deruxtecan-nxki injection for intravenous use – Daiichi Sankyo, Inc. and AstraZeneca Pharmaceuticals)

DATE REVIEWED: 12/20/2019

OVERVIEW

Enhertu is indicated for the treatment of adult patients with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer 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. Enhertu cannot be substituted for or with trastuzumab or Kadcyla (ado-trastuzumab emtansine).

Guidelines

According to the National Comprehensive Cancer Network (NCCN) breast cancer guidelines (version 2.2020 – February 5, 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; 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 Enhertu. 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. All approvals are provided for the duration noted below.

Automation: None.

Recommended Authorization Criteria

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

FDA-Approved Indications

30. Breast Cancer. Approve for 1 year if the patient meets ALL of the criteria (A, B, and C):
- **A)** The patient has unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive disease; AND
- **B)** The patient has received at least two prior anti-HER2-based regimens 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 prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Enhertu 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.

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

17. Enhertu™ for intravenous use [prescribing information]. Basking Ridge, NJ and Wilmington, DE: Daiichi Sankyo, Inc. and Astrazeneca Pharmaceuticals; December 2019.
18. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 2.2020 – February 13, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 13, 2020.

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351. 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.
352. 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.
353. 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.
354. 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.
355. 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.
356. 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.
357. 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.

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

14. Colon and Rectal Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
- **31.** Patient has advanced or metastatic disease; AND
- **32.** 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
- **33.** 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
- **34.** 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.

15. 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):
  - **i.** Erbitux will be used in combination with radiation therapy; OR
  - **ii.** Erbitux will be used in combination with platinum-based therapy; OR
    Note: Examples of platinum chemotherapy include cisplatin and carboplatin.
  - **iii.** 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

16. 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.

17. 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.

18. 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:

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

25. Erbitux® injection for intravenous infusion [prescribing information]. Indianapolis, IN: Eli Lilly and Company/ImClone LLC; April, 2019.
26. 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.
27. 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.

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

162. 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.

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

608. Erwinaze® injection for intramuscular or intravenous use [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals; December 2019.
609. 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.
610. 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.
611. 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.

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

163. 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

164. Mycosis Fungoides/Sezary Syndrome. Approve for 1 year if Folotyn is prescribed by or in consultation with an oncologist or dermatologist.

165. 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.

166. 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.

167. 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.

168. 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.

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

612. Folotyn® injection [prescribing information]. East Windsor, NJ: Acrotech Biopharma; May 2020.
613. 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.
614. 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.
615. 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.

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

19. Breast Cancer – Fulvestrant Monotherapy. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **35.** The medication is prescribed by or in consultation with an oncologist; AND
- **36.** Patient has recurrent or metastatic hormone receptor (HR)-positive (i.e., estrogen receptor- [ER] or progesterone receptor [PR]-positive) disease; AND
- **37.** 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.

20. 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

21. 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.

22. 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.

23. 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.)

1. 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
28. Faslodex® injection for intramuscular use [prescribing information]. Wilmington, DE: AstraZeneca; March 2019.
29. 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.
30. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Gazyva® (obinutuzumab injection for intravenous use – Genentech, Inc.)

REVIEW DATE: 10/09/2019

OVERVIEW

Gazyva is indicated for use:

- In combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia;
- In combination with bendamustine and followed by Gazyva monotherapy for the treatment of patients with follicular lymphoma who relapse or are refractory to a rituximab containing regimen;
- In combination with chemotherapy and followed by Gazyva monotherapy for patients achieving at least a partial remission, for the treatment of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) (version 1.2020 – August 23, 2019) recommends Gazyva as a single agent (category 2B) or in combination with chlorambucil, bendamustine, venetoclax (Category 2A), or ibrutinib (category 2B) for the first-line treatment of CLL/SLL without del(17p)/TP53 mutation; as a single agent or in combination with venetoclax for the first-line treatment of CLL/SLL with del(17p)/TP53 mutation (category 2A); and as a single agent for relapsed or refractory CLL/SLL without del(17p)/TP53 mutation (category 2A).[2,3]

The NCCN guidelines on B-Cell Lymphomas (version 4.2019 – June 18, 2019) 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), or bendamustine; 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.

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

169. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Approve for 6 months if the patient meets the following criteria (A and B):
- **A)** The patient is ≥ 18 years of age; AND
- **B)** Gazyva is prescribed by or in consultation with an oncologist.

170. Follicular Lymphoma. Approve for 6 months if the patient meets the following criteria (A, B, and C):
- **B)** The 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.
    (Note: Examples include CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone], CVP [cyclophosphamide, vincristine, and prednisone], or bendamustine); OR
  - **ii.** For maintenance treatment following Gazyva in combination with chemotherapy; OR
  - **iii.** The patient experienced an adverse event or intolerance to a rituximab product.
    (Note: Examples of adverse events or intolerance includes paraneoplastic pemphigus, Stevens-Johnson syndrome, Lichenoid Dermatitis, vesiculobullous dermatitis, toxic epidermal necrolysis);[2,4] AND
- **C)** Gazyva is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

171. 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)** The 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.** The patient experienced an adverse event or intolerance to a rituximab product.
    (Note: Examples of adverse events or intolerance includes paraneoplastic pemphigus, Stevens-Johnson syndrome, Lichenoid Dermatitis, vesiculobullous dermatitis, toxic epidermal necrolysis];[2,4] AND
- **C)** Gazyva is prescribed by or in consultation with an oncologist.

172. 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)** The patient is ≥ 18 years of age; AND
- **B)** The patient experienced an adverse event or intolerance to a rituximab product.
  (Note: Includes paraneoplastic pemphigus, Stevens-Johnson syndrome, Lichenoid Dermatitis, vesiculobullous dermatitis, toxic epidermal necrolysis);[2,4] AND
- **C)** Gazyva is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Gazyva 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.

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

616. Gazyva® [prescribing information]. South San Francisco, CA: Genentech, Inc.; November 2017.
617. The NCCN Drugs and Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 30, 2019. Search term: obinutuzumab.
618. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma 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 August 30, 2019.
619. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 4.2019 – June 18, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 30, 2019.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Gonadotropin-Releasing Hormone Analogs

- Eligard® (leuprolide acetate for subcutaneous injection – Tolmar Pharmaceuticals Inc.)
- Firmagon® (degarelix for subcutaneous injection – Ferring Pharmaceuticals Inc.)
- Trelstar® (triptorelin pamoate for intramuscular injection – Allergan Inc.)

DATE REVIEWED: 12/04/2019

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. Table 1 has the approved doses for the three agents.

Table 1. Recommended FDA-Approved Dosages.[1-3]

Drug	Route of Administration	Dose and Frequency
Eligard	Subcutaneous	• 7.5 mg every month • 22.5 mg every 3 months • 30 mg every 4 months • 45 mg every 6 months
Firmagon	Subcutaneous	• Starting dose of 240 mg given as two injections of 120 mg • First maintenance dose (80 mg) given 28 days after the starting dose • Maintenance dose of 80 mg as one injection given every 28 days
Trelstar	Intramuscular	• 3.75 mg every 4 weeks • 11.25 mg every 12 weeks • 22.5 mg every 24 weeks

The National Comprehensive Cancer Network (NCCN) Guidelines for Head and Neck Cancer (version 3.2019 – September 16, 2019) 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]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Eligard, Trelstar, and Firmagon. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Eligard, Trelstar, and Firmagon 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

173. Prostate Cancer. Approve Eligard, Firmagon, or Trelstar for 1 year if prescribed by, or in consultation with, an oncologist.[1-3,5]

Other Uses with Supportive Evidence

174. Head and Neck Cancer – Salivary Gland Tumors. Approve Eligard for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** The patient has recurrent disease with distant metastases; AND
- **B)** The 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

Eligard, Trelstar, or Firmagon 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. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

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

620. Eligard® Subcutaneous Injection [prescribing information]. Fort Collins, CO: Tolmar Pharmaceuticals Inc.; April 2019.
621. Firmagon® Subcutaneous Injection [prescribing information]. Parsippany, NJ: Ferring Pharmaceuticals Inc.; May 2017.
622. Trelstar® Intramuscular Injection [prescribing information]. Madison, NJ: Allergan; January 2018.
623. The NCCN Head and Neck Cancer Clinical Practice Guidelines in Oncology (Version 3.2019 – September 16, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 29, 2019.
624. The NCCN Drugs and Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on November 29, 2019. Search terms: leuprolide acetate, degarelix, triptorelin pamoate.

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.

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

358. Halaven® Intravenous Infusion [prescribing information]. Woodcliff Lake, NJ: Eisai Inc.; October 2016
359. 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.
360. 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.
361. 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™ (trastuzumab and hyaluronidase-oysk for subcutaneous use – Genentech, Inc.)

DATE REVIEWED: 03/25/2020

OVERVIEW

Herceptin Hylecta is indicated in breast cancer for the following uses[1]:

1) 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.

2) Metastatic breast cancer 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 NCCN Breast Cancer clinical practice guidelines (version 3.2020 – March 6, 2020) 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. 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. All approvals are provided for the duration noted below.

Automation: None.

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

FDA-Approved Indications

31. Breast Cancer. Approve for the duration noted below if the patient meets ALL of the criteria (A, B, and C):
- **A)** The patient has human epidermal growth factor receptor 2 (HER2)-positive disease; AND
- **B)** The 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
- **C)** The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Herceptin Hylecta 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
19. Herceptin Hylecta™ for subcutaneous use [prescribing information]. South San Francisco, CA: Genentech, Inc.; February 2019.
20. 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 March 16, 2020.
21. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 16, 2020. Search term: trastuzumab hyaluronidase.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Imfinzi Prior Authorization Policy
- Imfinzi® (durvalumab injection for intravenous use – AstraZeneca)

REVIEW DATE: 07/15/2020

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.

- **Urothelial carcinoma,** in adult patients with locally advanced or metastatic disease with 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.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on bladder cancer (version 5.2020 – May 12, 2020) recommends Imfinzi as one of the options for subsequent therapy (category 2A), as an alternative preferred regimen for the treatment of locally advanced or metastatic urothelial carcinoma after progression on platinum-based chemotherapy or disease that has progressed within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.[2,3] Imfinzi can be used regardless of PD-L1 expression levels.

The 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.

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

6. 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.

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 Imfinzi is not recommended in the following situations:

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

REFERENCES

31. Imfinzi® injection for intravenous use [prescribing information]. Wilmington, DE: AstraZeneca; June 2020.
32. 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 July 10, 2020.
33. 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.
34. 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.
35. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Imlygic® (talimogene laherparepvec intralesional injection – Amgen)

REVIEW 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

F) 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.

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® (ixabepilone injection for intravenous use – R-Pharm US)

DATE REVIEWED: 12/18/2019

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 3.2019 – September 6, 2019) 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

175. Breast Cancer. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** The patient has recurrent or metastatic disease; AND
- **B)** Ixempra is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Ixempra 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.

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

625. Ixempra® injection for intravenous use [prescribing information]. Princeton, NJ: R-Pharm US; January 2016.
626. The NCCN Drugs & Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on November 25, 2019. Search term: ixabepilone.
627. The NCCN Breast Cancer Clinical Practice Guidelines (Version 3.2019 – September 6, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 25, 2019.

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.

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

REFERENCES

362. Jevtana™ Intravenous Infusion [prescribing information]. Bridgewater, NJ: Sanofi-Aventis; January 2018.
363. 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.
364. 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.

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

32. 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.

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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

OVERVIEW

Keytruda, a human programmed death receptor-1 (PD-1) blocking antibody, is indicated for the treatment of the following indications:[1]

- **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.
- **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 programmed death-ligand 1 (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.
- **Head and neck squamous cell carcinoma** (HNSCC), 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 (combined positive score [CPS] ≥ 1) as determined by an FDA-approved test.
- **Classical Hodgkin lymphoma** (cHL), for treatment of adult and pediatric patients with refractory disease, or who have relapsed after three or more prior lines of therapy.*
- **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.
- **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 (Combined Positive Score [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.
- **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 (CRC) 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 (CNS) cancers have not been established.

- **Gastric cancer**, for treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (Combined Positive Score [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.*
- **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.*
- **Hepatocellular carcinoma**, for treatment of patients who have been previously treated with Nexavar® (sorafenib tablets).*
- **Merkel cell carcinoma**, for adult and pediatric patients with recurrent, locally advanced, or metastatic 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.*
- **Renal cell carcinoma**, in combination with Inlyta (axitinib tablets), for the first-line treatment of patients with advanced disease.
- **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.
- **Endometrial cancer**, in combination with Lenvima (lenvatinib capsules), for the treatment of patients with advanced disease that is not MSI-H or 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. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Dosing

The recommended dose of Keytruda is 200 mg (for pediatric patients, 2 mg/kg up to 200 mg) administered as an intravenous infusion once every 3 weeks or 400 mg given once every 6 weeks. It is given until disease progression or unacceptable toxicity, (or up to 24 months in patients with non-melanoma indications without disease progression). There are no recommended dose reductions in the prescribing information. Management of adverse events may require that Keytruda be withheld or permanently discontinued as determined by the prescribing physician.

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

1. **Cervical Cancer.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   - **B)** Patient has tried chemotherapy; AND
     Note: Examples of chemotherapy are cisplatin, paclitaxel, bevacizumab, topotecan, carboplatin).
   - **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)** 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.**

2. **Classic Hodgkin Lymphoma.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   - **A)** ONE the following conditions apply (i, ii, or iii):
     - **i.** Patient has had a hematopoietic stem cell transplantation (HSCT); OR
     - **ii.** Patient has tried three or more systemic regimens; OR
       Note: Examples of systemic therapies include 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]). This includes an auto-HSCT as one line of therapy.
     - **iii.** Patient is not eligible for transplant according to the prescriber; AND
   - **B)** The medication is prescribed by or in consultation with an oncologist.

3. **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.**

4. **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.**

5. **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.**

6. **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.
Note: Examples of platinum-contain chemotherapy regimens are: cisplatin or carboplatin with Erbitux® [cetuximab intravenous infusion], gemcitabine, or 5-fluorouracil [5-FU]; AND

C) The medication is prescribed by or in consultation with an oncologist.

7. 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.

8. 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.

9. 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.

10. Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors. Note**:** Examples of solid tumors with MSI-H or dMMR are breast, gastric, gastroesophageal or esophageal cancers, colon or rectal cancer, Ewing sarcoma, osteosarcoma, mesenchymal chondrosarcoma, poorly differentiated neuroendocrine tumor, pancreatic adenocarcinoma, endometrioid carcinomas, 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 colon or rectal cancer, and ONE of the following apply (a or b):

a) Patient has tried chemotherapy; OR
Note: Examples of chemotherapy are a fluoropyrimadine such as fluorouracil (5-FU), capecitabine; an adjunctive chemotherapy regimen such as FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).

b) Patient has metastatic disease and is not a candidate for intensive therapy, according to the prescriber; AND

B) The medication is prescribed by or in consultation with an oncologist.

11. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient has advanced or metastatic disease; AND
B) The tumor proportion score (TPS) for PD-L1 as determined by an approved test is ≥ 1%; AND
C) If the patient has non-squamous cell carcinoma (that is, adenocarcinoma, large cell, or NSCLC not otherwise specified) and the tumor is positive for a targetable mutation, the patient has previously received targeted drug therapy for the specific mutation; AND
Note: Examples of targetable 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.
D) Keytruda is prescribed by or in consultation with an oncologist.

12. 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.

13. 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) Keytruda is used in combination with Inlyta (axitinib tablets); AND
C) The medication is prescribed by or in consultation with an oncologist.

14. 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.

15. 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.
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

16. 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.

17. 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.

18. 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.

19. Mycosis Fungoides/Sezary Syndrome. Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

20. 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.

21. 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.

22. 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.**

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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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

176. 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.

164. Re-treatment with Kymriah. Kymriah is for one time use, repeat dosing is not approvable.

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

628. Kymriah™ suspension for intravenous infusion [prescribing information]. East Hanover, NJ: Novartis Oncology; May 2018.
629. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med*. 2018;378:439-448.
630. Schuster SJ, Bishop MR, Tam CS, et al. Primary analysis of Juliet: a global, pivotal, phase 2 trial of CTL019 in adult patients with relapsed or refractory diffuse large b-cell lymphoma. *Blood*. 2017;130(Suppl 1):577. Available at: http://www.bloodjournal.org/content/130/Suppl_1/577. Accessed on June 4, 2018.
631. 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 April 17, 2020.
632. 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: tisagenlecleucel.

633. 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.
634. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Kyprolis (carfilzomib injection for intravenous use – Amgen/Onyx Pharmaceuticals)

DATE REVIEWED: 02/26/2020

OVERVIEW

Kyprolis is an irreversible proteasome inhibitor that inhibits proteasome activity in blood and tissue and delays tumor growth.[1] It is indicated for treatment of multiple multiple myeloma in the following situations:

1. for relapsed or refractory multiple myeloma, in combination with dexamethasome ± Revlimid® (lenalidomide capsules) in patients who have received one to three lines of previous therapy; AND
2. for relapsed or refractory multiple myeloma, as a single agent for the treatment of those who have received one or more lines of therapy.

Safety and efficacy is not established in patients < 18 years of age.

Guidelines

The NCCN Multiple Myeloma clinical practice guidelines (version 2.2020 – October 9, 2020) recommend Kyprolis in treatment regimens for patients who are transplant and non-transplant candidates.[3] Kyprolis/Revlimid/dexamethasone is recommended as an Other Recommended Regimen for primary treatment in transplant candidates. In non-transplant candidates, Kyprolis/dexamethasone plus Revlimid or cyclophosphamide is a recommended Other Recommended Regimen for primary treatment. For previously treated multiple myeloma, Kyprolis/dexamethasone/Revlimid is among the Preferred regimens, whereas Kyprolis/dexamethasone ± cyclophosphamide, Kyprolis/Farydak (panobinostat capsules), and Kyprolis/dexamethasone/Pomalyst (pomalidomide capsules) are listed as Other Recommended Regimens.

In NCCN guidelines for Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lympohoma (version 2.2019), Kyprolis/Rituxan (rituximab infusion)/dexamethasone is listed among other recommended regimens for primary treatment of Waldenstrom's Magroglobulinemia/lymphoplasmacytic lymphoma.[4]

POLICY STATEMENT

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

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

24. Multiple Myeloma. Approve for 1 year if the patient meets BOTH of the following (A and B):
- **38.** The patient meets ONE of the following (i or ii):
  - **A)** Kyprolis will be used in combination with Revlimid (lenalidomide capsules) and dexamethazone OR
  - **B)** The patient has received at least ONE prior regimen for multiple myeloma.
    Note: Examples include regimens containing Velcade (bortezomib injection), Revlimid (lenalidomide capsules), Darzalex (daratumumab injection), Ninlaro (ixazomib capsules); AND
- **39.** The agent is prescribed by or in consultation with an oncologist or a hematologist.

Other Uses with Supportive Evidence

25. Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma. Approve for 1 year if the patient meets BOTH of the following (A and B):
- **A)** The agent will be used in combination with a rituximab product and dexamethasone; AND
- **B)** The agent is prescribed by or in consultation with an oncologist or a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Kyprolis 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.

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

36. Kyprolis® injection for intravenous use [prescribing information]. Onyx Pharmaceuticals/Amgen: Thousand Oaks, CA.; October 2019.
37. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 17, 2019. Search term: carfilzomib.
38. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (Version 2.2020 – October 9, 2020). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 17, 2020.
39. The NCCN Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma Clinical Practice Guidelines in Oncology (Version 1.2020 – December 6, 2019). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed February 18, 2020.
40. Treon SP, Tripsas CK, Meid K, et al. Carfilzomib, rituximab, and dexamethasone (CaRD) treatment offers a neuropathy-sparing approach for treating Waldenström's macroglobulinemia. *Blood*. 2014;124(4):503-510.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Lartruvo™ (olaratumab injection for intravenous use – Eli Lilly and Company)

REVIEW DATE: 10/09/2019

OVERVIEW

Lartruvo is a recombinant human IgG1 monoclonal antibody that binds to human platelet-derived growth factor receptor alpha (PDGFR-α).[1] PDGFR-α is a receptor tyrosine kinase that is involved in cell growth, chemotaxis, and mesenchymal stem cell differentiation. The receptor has been found on some tumors, including sarcomas, where signaling can contribute to cell proliferation, metastasis, and maintenance of the tumor microenvironment. Lartruvo prevents binding of PDGFR-α by the PDGF-AA and -BB ligands which prevents receptor activation and downstream PDGFR-α pathway signaling.

Lartruvo, is indicated, in combination with doxorubicin for the treatment of adults with soft tissue sarcoma with a subtype that an anthracycline-containing regimen is appropriate and which is not amenable to curative surgery or radiotherapy.[1]

The FDA granted accelerated approval to Lartruvo in October 2016 with the condition that a larger trial be conducted to confirm the safety and efficacy in patients with soft tissue sarcoma.[2] This study was completed and did not meet the primary endpoint of an improvement in overall survival for Lartruvo plus doxorubicin compared with placebo plus doxorubicin (the results are not currently available). In response to these results, the FDA recommends that Lartruvo not be started in new patients outside of a clinical trial and those currently receiving Lartruvo should discuss with their physician whether to remain on treatment.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on Soft Tissue Sarcoma (Version 2.2019 – February 4, 2019) removed Lartruvo in combination with doxorubicin as a treatment option for soft tissue sarcoma.[3]

The NCCN guidelines on Uterine Neoplasms (Version 3.2019 – February 11, 2019) removed Lartruvo in combination with doxorubicin as a treatment option for uterine sarcoma.[4]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Lartruvo. 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 Lartruvo as well as the monitoring required for adverse events and long-term efficacy, approval requires Lartruvo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

177. Soft Tissue Sarcoma.[2,3] Approve for 6 months if the patient meets the following criteria (A, B, and C):

- **A)** The patient is currently receiving Lartruvo; AND
- **B)** The patient has soft tissue sarcoma of extremity/superficial trunk, head/neck, retroperitoneal/intra-abdominal, angiosarcoma, pleomorphic rhabdomyosarcoma, or uterine; AND
- **C)** Lartruvo is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Lartruvo 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.)

167. Initiating therapy on Lartruvo. The FDA recommends that Lartruvo not be started in new patients outside of a clinical trial.[2]

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

635. Lartruvo™ injection for intravenous use [prescribing information]. Indianapolis, IN: Eli Lilly and Company; August 2018.
636. Olaratumab (Lartruvo) [press release]. Food and Drug Administration; January 24, 2019. Available at: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm526087.htm. Accessed on February 19, 2019.
637. 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 February 19, 2019.
638. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (Version 1.2019). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 19, 2019.

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

178. 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.

179. 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.

180. Methotrexate Overdosage, or Impaired Methotrexate Elimination. Approve for 1 month.

Other Uses with Supportive Evidence

181. 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.

182. 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.

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
639. Fusilev® injection for intravenous use [prescribing information]. Irvine, CA: Spectrum Pharmaceuticals; January 2020.
640. Khapzory™ injection for intravenous use [prescribing information]. Irvine, CA: Spectrum Pharmaceuticals; March 2020.
641. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Libtayo® (cemiplimab-rwlc injection, for intravenous use – Regeneron/Sanofi Genzyme)

REVIEW DATE: 10/02/2019

OVERVIEW

Libtayo, a programmed death receptor-1 (PD-1) blocking antibody, is indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for surgery or curative radiation.[1] Libtayo is a recombinant human immunoglobulin G4 (IgG4) monoclonal antibody that binds to PD-1 and blocks its interaction with PD-L1 and PD-L2, thereby releasing the PD-1 pathway-mediated inhibition of the immune response.

GUIDELINES

According to the National Comprehensive Cancer Network (NCCN) guidelines (version 2.2019 – October 23, 2018) 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.[2] 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. In a footnote, the guidelines note that Libtayo may be considered as a systemic therapy option for patients with locally advanced or metastatic cutaneous squamous cell carcinoma, who are not candidates for curative surgery or radiation therapy. Prior to Libtayo there were no systemic therapy options FDA-approved for the treatment of CSCC.

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 1 year in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

140. Cutaneous Squamous Cell Carcinoma (CSCC). Approve for 1 year if the patient meets ALL of the following (A, B and C):

A) The patient has locally advanced or metastatic CSCC; AND

B) The patient is not a candidate for curative surgery or curative radiation; AND
C) The medication is prescribed by, or in consultation with, an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Libtayo 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.

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

REFERENCES

388. Libtayo® injection for intravenous use [prescribing information]. Tarrytown, NY: Regeneron/Sanofi Genzyme; September 2018.
389. NCCN Squamous Cell Skin Cancer Clinical Practice Guidelines in Oncology (Version 2.2019 – October 23, 2018). ©2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 30, 2019.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Lumoxiti PA Policy (moxetumomab pasudotox-tdfk injection for intravenous use - AstraZeneca)

REVIEW DATE: 09/25/2019

OVERVIEW

Lumoxiti is a CD22-directed cytotoxin.[1] Lumoxiti is produced in *E. coli* via recombinant DNA technology and consists of a recombinant, murine immunoglobulin variable region fused to a shortened form of the *Pseudomonas* endotoxin, E38. Lumoxiti binds to the CD22 antigen on the cell surface and is internalized by the B-cell which results in ADP-ribosylation of elongation factor 2, inhibition of protein synthesis and apoptotic cell death.

Lumoxiti 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 3.2019 – January 31, 2019) recommends purine nucleoside analogs (cladribine and/or pentostatin) as first-line agents and Lumoxiti as a single agent for progression of hairy cell leukemia after therapy for relapsed/refractory disease.[2,3]

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

26. Hairy Cell Leukemia.

Criteria. 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. (Note: Purine analogs include cladribine and pentostatin); AND
O) Patient has an estimated creatinine clearance ≥ 30 mL/min; AND
P) Lumoxiti is prescribed by or in consultation with an oncologist.[1-3]

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Lumoxiti 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

642. Lumoxiti™ injection for intravenous use [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals; January 2019.
643. The NCCN Hairy Cell Leukemia Clinical Practice Guidelines in Oncology (Version 3.2019 – January 31, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed August 16, 2019.
644. The NCCN Drugs and Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 16, 2019. Search term: moxetumomab.

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

183. 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:

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

645. Monjuvi® intravenous infusion [prescribing information]. Boston, MA: Morphosus US/Incyte; July 2020.
646. 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.

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

27. **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.

28. 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

29. 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.

30. 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:

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

647. Mylotarg™ for intravenous infusion [prescribing information]. Philadelphia, PA: Pfizer; June 2020.
648. 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.
649. 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.

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

184. Acute Lymphoblastic Leukemia. Approve for 1 year if Oncaspar is prescribed by or consultation with an oncologist.

Other Uses with Supportive Evidence

185. Extranodal NK/T-cell Lymphoma, Nasal Type. Approve for 1 year if Oncaspar is prescribed by or in consultation with an oncologist.

186. 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.

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

REFERENCES
650. Oncaspar® injection for intramuscular and intravenous use [prescribing information]. Boston, MA: Servier Pharmaceutics; August 2019.
651. 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.
652. 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.
653. 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.
654. 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.

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

187. 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.

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

655. Onivyde® liposome injection [prescribing information]. Basking Ridge, NJ: Ipsen Biopharmaceuticals; June 2017.
656. The NCCN Pancreatic Adenocarcinoma Clinical Practice Guidelines in Oncology (Version 1.2020 – November 26, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed April 17, 2020.
657. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Opdivo Prior Authorization Policy

- Opdivo® (nivolumab injection for intravenous use – Bristol-Myers Squibb)

REVIEW DATE: 12/18/2019; selected revision 06/24/2020

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.**
- **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
  - Lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting.
- **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.
- **Small cell lung cancer**, in patients with metastatic disease with progression after platinum-based chemotherapy and at least one other line of therapy.[**]
- **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 progression-free survival (PFS). 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 overall response rate (ORR) and duration 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 Opdivo. 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. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

4. **Classic Hodgkin Lymphoma (cHL).** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) ONE the following conditions applies (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

B) The medication is prescribed by or in consultation with an oncologist.

5. **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) One of the following applies (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. The 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.

6. **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.

7. **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.

8. **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) [e.g., Nexavar {sorafenib tablets}, Lenvima {levatinib capsules}]; AND
   H) The medication is prescribed by or in consultation with an oncologist.

9. **Melanoma** [Note: This includes cutaneous melanoma, brain metastases due to melanoma, and uveal melanoma]. Approve for the duration noted 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 of treatment (total) if Opdivo will be used as adjuvant treatment (e.g., in a patient with no evidence of disease following resection of node-positive disease, locoregional recurrence, or in-transit recurrence); AND
   B) The medication is prescribed by or in consultation with an oncologist.

10. Non-Small Cell Lung Cancer (NSCLC). Approve for 1 year if the patient meets ALL of the following (A, B, and C):
- **A)** The medication is prescribed by or in consultation with an oncologist; AND
- **B)** Patient has advanced or metastatic disease; AND
- **C)** Patient meets one of the following (i or ii):
  - **i.** Opdivo is used as first-line therapy and the patient meets all of the following (a, b, and c):
    - **a)** Patient's 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)** Patient's tumor is negative for a targetable mutation; OR
      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.
  - **ii.** 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 non-squamous cell carcinoma (that is, adenocarcinoma, large cell, or NSCLC not otherwise specified) AND the patient's tumor is positive for a targetable mutation, the patient has received targeted drug therapy for the specific mutation.
      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.

11. Renal Cell Carcinoma. Approve for 1 year if the patient meets BOTH of the following (A and B):
- **A)** Patient has advanced (e.g., relapsed, Stage IV, or metastatic) disease; AND
- **B)** The medication is prescribed by or in consultation with an oncologist.

12. Small Cell Lung Cancer. 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 are cisplatin, carboplatin, etoposide, irinotecan, topotecan, paclitaxel.
- **B)** The medication is prescribed by or in consultation with an oncologist.

13. 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

14. **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.

15. **Extranodal NK/T-Cell Lymphoma, Nasal Type.** Approve for 1 year if the patient meets the following criteria (A and B):
    A) Patient has received an asparaginase-based chemotherapy regimen.
    Note: Examples of asparaginase-based chemotherapy are dexamethasone, ifosfamide, pegaspargase, etoposide; and gemcitabine, pegaspargase, oxaliplatin; AND
    B) The medication is prescribed by or in consultation with an oncologist.

16. **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.

17. **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) plus cisplatin or carboplatin, Alimta with cisplatin and bevacizumab, gemcitabine plus cisplatin, Alimta alone, vinorelbine.
    B) The medication is prescribed by or in consultation with an oncologist.

18. **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.

19. **Small Bowel Adenocarcinoma.** Approve for 1 year if the patient meets the following criteria (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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Opdivo is not recommended in the following situations:

82. 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. Opdivo® injection [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; June 2020.
31. The NCCN Hodgkin Lymphoma Clinical Practice Guidelines in Oncology (Version 2.2019 – July 15, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 17, 2019.
32. The NCCN Drugs & Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 8, 2020. Search term: nivolumab.
33. The NCCN Head and Neck Cancers Clinical Practice Guidelines in Oncology (Version 3.2019 – September 16, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 17, 2019.
34. The NCCN Hepatobiliary Cancer Clinical Practice Guidelines in Oncology (Version 3.2019 – August 1, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 17, 2019.
35. The NCCN Melanoma Clinical Practice Guidelines in Oncology (Version 3.2019 – October 22, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 17, 2019.
36. The NCCN Uveal Melanoma Clinical Practice Guidelines in Oncology (Version 1.2019 – June 14, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 8, 2019.
37. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 4.2019 – November 8, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 17, 2019.
38. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (Version 3.2019 – September 26, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 17, 2019.
39. 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.
40. 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 December 17, 2019.
41. The NCCN Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 2.2020 – November 15, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 17, 2019.
42. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (Version 1.2020 – November 27, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 17, 2019.
43. The NCCN Anal Carcinoma Clinical Practice Guidelines in Oncology (Version 1.2020 – November 19, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 17, 2019.
44. The NCCN Gestational Trophoblastic Neoplasia Cancer Clinical Practice Guidelines in Oncology (Version 1.2020 – December 11, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 11, 2019.
45. The NCCN Malignant Pleural Mesothelioma Clinical Practice Guidelines in Oncology (Version 1.2020 – November 27, 2019) © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 17, 2019.
46. 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 on December 17, 2019.
47. The NCCN Small Bowel Adenocarcinoma Clinical Practice Guidelines in Oncology (Version 1.2020 – July 30, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 17, 2019.
48. 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 June 8, 2020.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Padcev™ (enfortumab vedotin – ejfv injection for intravenous use – Astellas Pharma and Seattle Genetics)

DATE REVIEWED: 12/20/2019

OVERVIEW

Padcev is an antibody-drug conjugate which contains the fully human anti-Nectin-4 monoclonal antibody conjugated to the microtubule disrupting agent, monomethyl auristatin E.[1]

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 guidelines (version 2.2020 – January 7, 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

188. Urothelial Carcinoma. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):

- **A)** The patient is ≥ 18 years of age; AND
- **B)** The patient has locally advanced or metastatic disease; AND
- **C)** The patient has previously received a programmed death receptor-1 or programmed death-ligand 1 inhibitor (checkpoint inhibitors), unless the prescriber determines the patient is not eligible for checkpoint inhibitor therapy.
  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); AND
- **D)** The patient has previously received platinum-containing chemotherapy, unless the prescriber determines the patient is not eligible for platinum chemotherapy.
  Note: Examples include cisplatin, carboplatin, and oxaliplatin; AND
- **E)** Padcev is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Padcev 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.

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

658. Padcev™ for injection for intravenous use [prescribing information]. Northbrook, IL: Astellas Pharma; December 2019.
659. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (version 2.2020 – January 7, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 14, 2020.
660. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 14, 2020. Search term: enfortumab.

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

33. 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
369. Perjeta® injection, for intravenous use [prescribing information]. South San Francisco, CA: Genentech, Inc.; January 2020.
370. 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.
371. 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.
372. 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.
373. 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.

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

34. 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:

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
22. Phesgo™ injection for subcutaneous use [prescribing information]. South San Francisco, CA: Genentech, Inc.; June 2020.
23. 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.

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

189. 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

190. 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:

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
661. Polivy™ injection for intravenous use [prescribing information]. South San Francisco, CA: Genentech; June 2019.
662. 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.
663. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Portrazza® (necitumumab injection for intravenous use – Eli Lilly)

DATE REVIEWED: 01/15/2020

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 2.2020 – December 23, 2019) notes that Portrazza/cisplatin/gemcitabine in the first-line setting is not used at NCCN member institutions due to the efficacy and safety of this agent compared to the efficacy/safety of other available agents.[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

40. Non-Small Cell Lung Cancer (NSCLC). Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** The 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
Portrazza 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.

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
374. Portrazza® Intravenous Infusion [prescribing information]. Indianapolis, IN: Eli Lilly and Company; November 2015.
375. 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 on January 13, 2020.

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

141. 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

142. 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:

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

REFERENCES

390. Poteligeo® injection [prescribing information]. Bedminster, NJ: Kyowa Kirin, Inc.; August 2018.
391. 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.
392. 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.
393. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Proleukin® (aldesleukin injection for intravenous use – Prometheus Laboratories)

REVIEW DATE: 12/18/2019

OVERVIEW

Proleukin, a human recombinant interleukin-2 product, is indicated for the treatment of adults with metastatic renal cell carcinoma (mRCC), and adults with metastatic melanoma.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on Kidney Cancer (Version 2.2020 – August 5, 2019) 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]

The NCCN guidelines on Cutaneous Melanoma (Version 3.2019 – October 22, 2019) 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 guidelines on Hematopoietic Cell Transplantation (Version 1.2020 – October 30, 2019) recommend Proleukin as additional therapy, in combination with systemic corticosteroids, for steroid-refractory chronic graft-vs-host disease.[2,5]

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

191. Kidney Cancer. Approve for 6 months if the patient meets the following criteria (A, B, C, D, and E):
- **A)** The patient is ≥ 18 years of age; AND
- **B)** The patient has relapsed or metastatic disease; AND
- **C)** The 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.

192. Cutaneous Melanoma. Approve for the duration noted if the patient meets ONE of the following (A or B):
- **A)** Intravenous Therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv, and v):
  - **i.** The patient is ≥ 18 years of age; AND
  - **ii.** The patient has metastatic or unresectable disease; AND
  - **iii.** The 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 for 6 months if the patient meets the following criteria (i, ii, and iii):
  - **i.** The 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 agent is prescribed by or in consultation with an oncologist or dermatologist.

Other Uses with Supportive Evidence

193. Graft-versus-Host Disease. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):

A) The patient has chronic graft-vs-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

Proleukin 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.

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

664. Proleukin® injection for intravenous use [prescribing information]. San Diego, CA: Prometheus Laboratories Inc.; August 2018.
665. The NCCN Drugs and Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on November 18, 2019. Search term: aldesleukin.
666. The NCCN Kidney Cancer Clinical Practice Guidelines (Version 2.2020 – August 5, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 18, 2019.
667. The NCCN Cutaneous Melanoma Clinical Practice Guidelines (Version 3.2019 – October 22, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 18, 2019.
668. The NCCN Hematopoietic Cell Transplantation Clinical Practice Guidelines (Version 1.2020 – October 30, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 18, 2019.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Rituxan Hycela™ (rituximab and hyaluronidase human injection for subcutaneous use – Biogen and Genentech/Roche)

REVIEW DATE: 10/16/2019

OVERVIEW

Rituxan Hycela is indicated for treatment of adults with the following indications:

1. **Follicular lymphoma** (FL), as a single agent for relapsed or refractory disease; in previously untreated FL 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) FL;
2. **Diffuse large B-cell lymphoma** (DLBCL), in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or other anthracycline-based chemotherapy regimens in patients with previously untreated disease; and
3. **Chronic lymphocytic leukemia** (CLL), in combination with FC (fludarabine + cyclophosphamide) for previously treated and previously untreated disease.[1]

Rituxan Hycela is a combination of rituximab and hyaluronidase human. It contains the identical molecular antibody of rituximab available in Rituxan IV, 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 (BSA); dose reductions are not recommended. When given in combination with chemotherapy, reduce the dose of chemotherapeutic drugs to manage adverse events (AEs). Rituxan Hycela is not indicated for treatment of non-malignant conditions.

Disease Overview

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of lymphoproliferative disorders originating in B-lymphocytes.[2] Major subtypes of NHL diagnosed in the US include DLBCL (33% of NHL cases), CLL/small lymphocytic lymphoma (SLL) [19% of NHL cases], and FL (17% of NHL cases). Cell-surface proteins, including CD20, are highly expressed on these B-cell malignancies.[3] Rituxan Hycela is an anti-CD20 monoclonal antibody that, upon binding to CD20 on B-lymphocytes, depletes B cells by several mechanisms, including direct antibody-dependent cellular toxicity, complement-mediated cell death, and signaling apoptosis.

Guidelines

Rituximab features prominently in the National Comprehensive Cancer Network (NCCN) guidelines for treatment of B-cell lymphomas (version 4.2019 – June 18, 2019) and CLL/small lymphocytic lymphoma (version 1.2020 – August 23, 2019) and is included in multiple treatment regimens across the spectrum of disease. In hairy cell leukemia, NCCN 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. All of these guidelines 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 IV.

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 IV, which allows for management by slowing or stopping the IV infusion, before receiving Rituxan Hycela. Patients who are unable to complete one full IV infusion should continue to receive subsequent cycles with rituximab IV and should not switch to Rituxan Hycela until a full IV dose is successfully administered. Safety is otherwise comparable to rituximab IV and includes Boxed Warnings regarding severe mucocutaneous reactions, hepatitis B reactivation, and progressive multifocal leukoencephalopathy.

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 and long-term efficacy, initial 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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

143. Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL). Approve for 1 year if the patient meets the following criteria (A, B, and C):
A) The patient has already received at least one full dose of rituximab intravenous; AND
B) The agent is administered under the care of a healthcare professional; AND
C) The agent is being prescribed by or in consultation with an oncologist.

144. B-Cell Lymphoma (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). Approve for 1 year if the patient meets the following criteria (A, B, and C):
A) The patient has already received at least one full dose of rituximab intravenous; AND
B) The agent is administered under the care of a healthcare professional; AND
C) The agent is being prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

7. **Hairy Cell Leukemia.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   A) The patient has relapsed/refractory hairy cell leukemia; AND
   B) The patient has already received at least one full dose of rituximab intravenous; AND
   C) The agent is administered under the care of a healthcare professional; AND
   D) The agent is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Rituxan Hycela 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. **Granulomatosis with Polyangiitis (GPA) [Wegener's granulomatosis] or Microscopic Polyangiitis (MPA).** Rituximab IV is indicated for treatment of GPA or MPA.[5] Rituxan Hycela has not been evaluated and does not have established dosing for GPA or MPA.

86. **Pemphigus Vulgaris.** Rituximab IV is indicated for treatment of pemphigus vulgaris.[5] Rituxan Hycela has not been evaluated and does not have established dosing for pemphigus vulgaris.

87. **Rheumatoid Arthritis (RA).** Rituximab IV is indicated for treatment of RA.[5] Rituxan Hycela has not been evaluated and does not have established dosing for RA.

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

306. Rituxan Hycela™ injection for SC use [prescribing information]. South San Francisco, CA: Biogen and Genentech/Roche; April 2018.
307. The NCCN B-Cell Lymphoma Clinical Practice Guidelines in Oncology (Version 4.2019 – June 18, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 11, 2019.
308. Dotan E, Aggarwal C, Smith MR. Impact of rituximab (Rituxan) on the treatment of B-cell non-Hodgkin's lymphoma. *P T*. 2010; 35(3): 148–157.
309. The NCCN CLL/SLL 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 September 11, 2019.
310. Rituxan® intravenous infusion [prescribing information]. South San Fransisco, CA: Genentech, Inc.; April 2019.
311. The NCCN Primary Cutaneous Lymphomas Clinical Practice Guidelines in Oncology (Version 2.2019 – December 17, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 9, 2019.
312. 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 September 11, 2019.

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

194. 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.

195. 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.

196. 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

197. 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.

198. 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.

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

669. Istodax® injection for intravenous use. [prescribing information]. Summit, NJ: Celgene Corporation; November 2018.
670. 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.
671. 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.
672. 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.

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

31. Multiple Myeloma. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, E and F):
- **41.** The patient is ≥ 18 years of age; AND
- **42.** The agent will be used in combination with Pomalyst (pomalidomide capsules)and dexamethasone; AND
- **43.** 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
- **44.** 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
- **45.** Revlimid (lenalidomide capsules) was a component of at least one previous regimen; AND
- **46.** 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.

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

41. Sarclisa® injection [prescribing information]. Bridgewater, NJ: Sanofi-Aventis; March 2020.
42. 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.
43. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Sylatron™ (peginterferon alfa-2b injection for subcutaneous use - Merck)

DATE REVIEWED: 12/18/2019

OVERVIEW

Sylatron, a pegylated interferon alfa-2b product, is indicated for adjuvant treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) cutaneous melanoma (Version 3.2019 – October 22, 2019) clinical practice guidelines no longer recommend Sylatron for the treatment of melanoma.[2]

The NCCN systemic mastocytosis (Version 2.2019 – September 20, 2018) clinical practice guidelines recommend Sylatron alone or in combination with prednisone for the treatment of aggressive systemic mastocytosis and systemic

mastocytosis with an associated hematologic neoplasm when the systemic mastocytosis component needs more immediate treatment.[3,4] In addition, Sylatron is recommended for osteopenia/osteoporosis in patients with refractory bone pain and/or worsening bone mineral density on bisphosphonate therapy.

The NCCN myeloproliferative neoplasms (Version 3.2019 – September 4, 2019) clinical practice guidelines recommend Sylatron for the treatment of symptomatic low-risk myelofibrosis, polycythemia vera, and essential thrombocythemia.[4,5]

POLICY STATEMENT

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

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

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

199. Melanoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** The patient has microscopic or gross nodal involvement; AND
- **B)** The patient had complete lymphadenectomy within the past 84 days; AND
- **C)** Sylatron will be prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

200. Systemic Mastocytosis. Approve for 1 year if the patient meets the following (A and B):
- **A)** The patient has one of the following (i, ii, or iii):
  - **i.** Aggressive systemic mastocytosis; OR
  - **ii.** Systemic mastocytosis with an associated hematologic malignancy; OR
  - **iii.** Osteopenia/osteoporosis with refractory bone pain and/or decreasing bone mineral density on bisphosphonate therapy; AND
- **B)** Sylatron is prescribed by or in consultation with an oncologist.

201. Myeloproliferative Neoplasms. Approve for 1 year if the patient meets the following (A and B):
- **A)** The patient has one of the following (i, ii, or iii):
  - **i.** Symptomatic low-risk myelofibrosis; OR
  - **ii.** Polycythemia vera; OR
  - **iii.** Essential thrombocythemia; AND
- **B)** Sylatron is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Sylatron 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

673. Sylatron™ injection for subcutaneous use [prescribing information]. Whitehouse Station, NJ: Merck; August 2019.
674. The NCCN Cutaneous Melanoma Clinical Practice Guidelines (Version 3.2019 – October 22, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 19, 2019.
675. The NCCN Systemic Mastocytosis Clinical Practice Guidelines (Version 2.2019 – September 20, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 19, 2019.
676. The NCCN Drugs and Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on November 19, 2019. Search term: Sylatron.
677. The NCCN Myeloproliferative Neoplasms Clinical Practice Guidelines (Version 3.2019 – September 4, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 19, 2019.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Sylvant® (siltuximab intravenous infusion – Janssen Biotech, Inc.)

REVIEW DATE: 02/19/2020; selected revision 03/25/2020

OVERVIEW

Sylvant is an interleukin (IL)-6 antagonist 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 interleukin (IL)-6 in a nonclinical study, Sylvant has not been studied in patients with MCD who are HIV positive or HHV-8 positive. 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 1.2020 – January 22, 2020) 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

G) 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.** The patient is ≥ 18 years of age; AND
  - **ii.** The patient is negative for the human immunodeficiency virus (HIV) and human herpesvirus-8 (HHV-8); AND
  - **iii.** The patient meets ONE of the following (a or b):
    - **a)** The 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.
- **E)** 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

Sylvant 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. **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. 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

5. Sylvant® for intravenous injection [prescribing information]. Hemel Hempstead, Hertfordshire, UK: EUSA Pharma; December 2019.
6. 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.
7. The NCCN B-Cell 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 February 12, 2020.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. Centers for Disease Control and Prevention (Web site). Coronavirus (COVID-19). Updated March 22, 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/index.html/. Accessed on March 23, 2020.
14. US National Institutes of Health. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2020 Mar 23]. Available from: https://clinicaltrials.gov/ct2/results?cond=Coronavirus&term=tocilizumab&cntry=&state=&city=&dist=. Search terms: coronavirus, tocilizumab.
15. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Available at: file:///C:/Users/MMedina/Downloads/202003.00026v1%20(1).pdf. Accessed on March 23, 2020.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Synribo® (omacetaxine mepesuccinate injection for subcutaneous use – Teva)

REVIEW DATE: 09/04/2019

OVERVIEW

Synribo is indicated for the treatment of adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKIs).[1] Synribo can be administered by someone other than a healthcare professional (e.g., patient or a caregiver), if appropriate. The mechanism of action of Synribo has not been fully determined but involves inhibition of protein synthesis. The safety and efficacy of Synribo is 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 2019, it was estimated that 8,990 patients would be diagnosed in the US, and 1,140 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 on for CML (version 1.2020 – August 26, 2019) recommend Synribo as a treatment option for patients who have experienced disease progression to AP CML on TKI therapy.[2] It is not an option among patients who present with AP 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. 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 Indications

202. Chronic Myeloid Leukemia (CML). Approve for 6 months if the patient meets the following criteria (A, B, and C):

- **A)** Synribo is prescribed by or in consultation with an oncologist; AND
- **B)** The patient is ≥ 18 years of age; AND
- **C)** The patient meets one of the following criteria (i or ii):
  - **i.** The patient if T315I positive; OR
  - **ii.** The patient has tried at least two tyrosine kinase inhibitors indicated for use in CML (e.g., Gleevec® [imatinib tablets], Sprycel® [dasatinib tablets], Tasigna® [nilotinib capsules], Bosulif® [bosutinib tablets], Iclusig® [ponatinib tablets]).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Synribo 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.)

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

44. Synribo® injection for subcutaneous use [prescribing information]. North Wales, PS: Teva Pharmaceuticals; June 2017.
45. The NCCN Chronic Myeloid Leukemia Clinical Practice Guidelines in Oncology (Version 1.2020 – August 26, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 30, 2019.
46. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2018 update on diagnosis, therapy and monitoring. *Am J Hematol*. 2018;93:442-459.

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

203. 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:

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

678. Tecartus™ suspension for intravenous infusion [prescribing information]. Santa Monica, CA: Kite Pharma; July 2020.
679. 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.
680. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Tecentriq Prior Authorization Policy
- Tecentriq® (atezolizumab injection for intravenous use – Genentech/Roche)

REVIEW DATE: 11/13/2019; selected revisions 06/24/2020

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.
- **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
   - **B)** The tumor is programmed death-ligand 1 (PD-L1)-positive; AND
   - **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. **Non-Small Cell Lung Cancer.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **C)** Tecentriq is prescribed by or in consultation with an oncologist; AND
   - **D)** Patient has advanced or metastatic disease; AND
   - **E)** 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 targetable mutations; AND
  Note: Examples of targetable mutations include epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, *ROS1*, *BRAF*, *MET exon 14* skipping mutation, *RET* rearrangement.
- **b)** Patient meets one of the following [(1) or (2)]:
  - **(1)** Patient's tumor expresses programmed death-ligand 1 (PD-L1) ≥ 50% as determined by an approved test; OR
  - **(2)** The patient's tumor expresses programmed death-ligand 1 (PD-L1) ≥ 1% to 49% as determined by an approved test and Tecentriq will be used in combination with chemotherapy; OR
    Note: Examples of chemotherapy include bevacizumab, paclitaxel, and carboplatin, or carboplatin and Abraxane (paclitaxel, albumin-bound for injection).

ii. Patient has squamous cell NSCLC and meets both of the following (a and b):
- **a)** The tumor is negative for targetable mutations; AND
  Note: Examples of targetable mutations include epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, *ROS1*, *BRAF*, *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. Patient's tumor is positive for targetable mutations and the patient meets both of the following (a and b):
Note: Examples of targetable mutations include epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, *ROS1*, *BRAF*, *MET exon 14* skipping mutation, *RET* rearrangement.
- **a)** Patient has tried at least one of the targeted therapy options; AND
- **b)** Tecentriq will be used as subsequent therapy.

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 prescribing physician, 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 prescribing physician, the patient is not eligible for platinum-containing chemotherapy (i.e., cisplatin and carboplatin) [Note: this is regardless of the PD-L1 status]; OR

iii. Patient has tried at least one platinum- (cisplatin or carboplatin) containing chemotherapy; AND

J) Tecentriq is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tecentriq is not recommended in the following situations:

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

394. Tecentriq® injection for intravenous use [prescribing information]. South San Francisco, CA: Genentech, Inc (A member of the Roche Group); May 2020.
395. The NCCN Drugs & Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on June 8, 2020. Search term: atezolizumab.
396. 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.
397. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (Version 4.2019 – July10, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on November 11, 2019.
398. The NCCN Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 1.2020 – October 10, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on November 11, 2019.
399. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 3.2019 – September 6, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: www.nccn.org. Accessed on November 11, 2019.
400. 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 8, 2020.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Thiotepa injection for intravenous, intracavitary, or intravesical use (Tepadina® - Adienne SA, generics)

REVIEW DATE: 10/16/2019

OVERVIEW

Thiotepa is an alkylating agent indicated:

- 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 beta-thalassemia.[1]
- For the treatment of breast or ovarian adenocarcinoma.
- For controlling intracavitary effusions secondary to diffuse or localized neoplastic diseases of various serosal cavities.
- For the treatment of superficial papillary carcinoma of the urinary bladder.[1,2]

Guidelines

The National Comprehensive Cancer Network (NCCN) breast cancer guidelines (version 3.2019 – September 6, 2019) do not provide any recommendations on the use of thiotepa in the management of breast cancer.[3]

The NCCN ovarian cancer guidelines (version 2.2019 – September 17, 2019) do not provide any recommendations on the use of thiotepa in the management of ovarian cancer.[4]

The NCCN bladder cancer guidelines (version 4.2019 – July 10, 2019) state that intravesical thiotepa does not appear to be effective. NCCN recommends gemcitabine and mitomycin for intravesical chemotherapy.[5]

The NCCN central nervous system (CNS) cancers guidelines (version 2.2019 – September 16, 2019) 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.

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

204. Beta-Thalassemia. Approve for 1 month if the patient meets the following criteria (A, B, C, D, and E):
- **A)** The patient is ≤ 18 years of age; AND
- **B)** The 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)** Thiotepa is prescribed by or in consultation with an oncologist.

205. Breast Cancer. Approve for 6 months if thiotepa is prescribed by or in consultation with an oncologist.

206. Ovarian Cancer. Approve for 6 months if thiotepa is prescribed by or in consultation with an oncologist.

207. Bladder Cancer. Approve for 1 month if the patient meets the following criteria (A and B):
- **A)** The patient has superficial papillary carcinoma of the urinary bladder; AND
- **B)** Thiotepa is prescribed by or in consultation with an oncologist.

208. Malignant Effusions. Approve for 6 months if the patient meets the following criteria (A and B):
- **A)** The patient has intracavitary effusions secondary to diffuse or localized neoplastic disease; AND
- **B)** Thiotepa is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

209. 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)** Thiotepa is prescribed by or in consultation with an oncologist.

210. Leptomeningeal Metastases. Approve for 6 months if thiopeta is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Thiotepa 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.

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

681. Tepadina® injection [prescribing information]. Lugano, Switzerland: Adienne SA; January 2017.
682. Thiotepa for injection [prescribing information]. Schaumberg, IL: Sagent Pharmaceuticals; April 2018.
683. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 3.2019 – September 6, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed September 20, 2019.
684. The NCCN Ovarian Cancer Clinical Practive Guidelines in Oncology (Version 2.2019 – September 17, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at; http://www.nccn.org. Accessed September 20, 2019.
685. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (Version 4.2019 – July 10, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. accessed on September 20, 2019.
686. The NCCN Central Nervous System Cancers 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 September 20, 2019.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Topotecan Products

- Hycamtin® (topotecan capsule – Novartis)
- Topotecan injection for intravenous use (Hycamtin® – Novartis, generics)

DATE REVIEWED: 12/18/2019

OVERVIEW

Topotecan injection, a topoisomerase inhibitor, is indicated for the treatment of patients with:

- 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;
- Stage IV-B, recurrent, or persistent cervical cancer which is not amenable to curative treatment, in combination with cisplatin.[1]

Guidelines

The National Comprehensive Cancer Network (NCCN) ovarian cancer (Version 2.2019 – September 17, 2019) 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 SCLC (Version 2.2020 – November 15, 2019) 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 cervical cancer (Version 5.2019 – September 16, 2019) clinical practice guidelines recommend topotecan as first- or second-line therapy for patients with local/regional recurrence, stage IVB disease, or distant metastases.[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 uterine cancer (Version 4.2019 – September 16, 2019) clinical practice guidelines recommend topotecan as a single agent for the treatment of recurrent, metastatic, or high-risk endometrial carcinoma.[2,6]

The NCCN bone cancer (Version 1.2020 – August 12, 2019) 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 (CNS) cancers (Version 3.2019 – October 18, 2019) clinical practice guidelines recommend topotecan as a single agent for the treatment of relapsed or refractory primary CNS lymphoma and recurrent 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 Merkel cell carcinoma (Verison 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]

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

211. Ovarian, Fallopian Tube, and Primary Peritoneal Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** The 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.

212. Small Cell Lung Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** The patient meets one of the following (i or ii):
  - **i.** The patient has relapsed disease; OR
  - **ii.** The 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.

213. Cervical Cancer. 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.** The patient has local/regional recurrence; OR
  - **ii.** The patient has distant metastases; AND
- **B)** Topotecan is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

214. Endometrial Carcinoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** The 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.

215. Rhabdomyosarcoma. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** The patient has non-pleomorphic rhabdomyosarcoma; AND
- **B)** Topotecan is prescribed by or in consultation with an oncologist.

216. Bone Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):
- **A)** The 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)** The 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.

217. Primary Central Nervous System Lymphoma. 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)** Topotecan will be used as a single agent; AND
- **C)** Topotecan is prescribed by or in consultation with an oncologist.

218. Brain Metastatases. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** The patient has recurrent disease; AND
- **B)** The patient has small cell lung cancer; AND
- **C)** Topotecan will be used as a single agent; AND
- **D)** Topotecan is prescribed by or in consultation with an oncologist.

219. Leptomeningeal and Spinal Metastatases. 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.

220. **Merkel Cell Carcinoma**. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** The patient has distant metastatic disease; AND
- **B)** The patient has contraindications to checkpoint immunotherapy.
  Note: Checkpoint immunotherapy includes Bavencio® (avelumab injection for intravenous use), Keytruda® (injection for intravenous use), and Opdivo® (injection for intravenous use); AND
- **C)** Topotecan is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Topotecan 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.

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

687. Hycamtin injection for intravenous use [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals; October 2019.
688. The NCCN Drugs & Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on November 20, 2019. Search term: topotecan.
689. The NCCN Ovarian Cancer Clinical Practice Guidelines (Version 2.2019 – September 17, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 20, 2019.
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691. The NCCN Cervical Cancer Clinical Practice Guidelines (Version 5.2019 – September 16, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 21, 2019.
692. The NCCN Uterine Cancer Clinical Practice Guidelines (Version 4.2019 – September 16, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 22, 2019.
693. The NCCN Bone Cancer Clinical Practice Guidelines (Version 1.2020 – August 12, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 22, 2019.
694. The NCCN Central Nervous System Cancers Clinical Practice Guidelines (Version 3.2019 – October 18, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 22, 2019.
695. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Torisel (temsirolimus injection for intravenous use – Wyeth Pharmaceuticals)

REVIEW DATE: 10/16/2019

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 2.2020 – August 5, 2019) 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 4.2019 – September 12, 2019) recommend Torisel for the treatment of perivascular epithelioid cell tumors (PEComas), and lymphangioleiomyomatosis or angiomyolipomas.[2,4]

The NCCN guidelines for uterine neoplasms (Version 4.2019 – September 16, 2019) 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

221. Renal Cell Carcinoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** The patient has relapsed, advanced, or metastatic disease; AND
- **B)** Torisel will be used as a single-agent; AND
- **C)** Torisel is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

222. Soft Tissue Sarcoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** The 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)** Torisel is prescribed by or in consultation with an oncologist.

223. Endometrial Carcinoma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
- **A)** The patient has recurrent, metastatic, or high-risk disease; AND
- **B)** Torisel will be used as a single-agent; AND
- **C)** Torisel is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

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

REFERENCES
696. Torisel® injection for intravenous use [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals; March 2018.
697. The NCCN Drugs and Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 24, 2019.
698. 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 September 24, 2019.
699. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (Version 4.2019 – September 12, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 24, 2019.
700. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (Version 4.2019 – September 16, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 24, 2019.

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

35. 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.

36. 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.

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

24. Herceptin® for injection for intravenous use [prescribing information]. South San Francisco, CA: Genentech, Inc.; November 2018.
25. 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.
26. 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.
27. 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.
28. 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.

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

37. 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.

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
29. Trodelvy™ injection for intravenous use [prescribing information]. Morris Plains, NJ: Immunomedics, Inc.; April 2020.
30. 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.

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

32. 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:

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

REFERENCES

47. Vectibix® injection for intravenous infusion [prescribing information]. Thousand Oaks, CA: Amgen Inc; June 2017.
48. 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.
49. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Vyxeos (daunorubicin and cytarabine liposome for injection – Jazz Pharmaceuticals)

REVIEW DATE: 10/16/2019

OVERVIEW

Vyxeos is a liposomal combination of daunorubicin, an anthracycline topoisomerase inhibitor, and cytarabine, a nucleoside metabolic inhibitor, is indicated for the treatment of adults with newly-diagnosed therapy-related acute myeloid leukemia (AML) or AML with myelodysplasia-related changes.[1]

Guidelines

The National Comprehensive Cancer Network guidelines for acute myeloid leukemia 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

224. Acute Myeloid Leukemia. 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 meets one of the following (i or ii):
  - **i.** The patient has therapy-related acute myeloid leukemia; OR
  - **ii.** The patient has secondary acute myeloid leukemia.
    (Note: Examples include antecedent myelodysplastic syndrome/chronic myelomonocytic leukemia and acute myeloid leukemia with myelodysplasia-related changes); AND
- **C)** Vyxeos is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Vyxeos 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.

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

REFERENCES

701. Vyxeos liposome for injection [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals; August 2017.
702. The NCCN Drugs & Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 26, 2019. Search term: Vyxeos.
703. 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 September 26, 2019.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
New Policy	--	10/16/2019

* 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: Oncology (Injectable) – Yervoy® (ipilimumab injection for intravenous use – Bristol-Myers Squibb)

REVIEW DATE: 09/25/2019

OVERVIEW

Yervoy, a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody, is indicated for the following conditions:

1) Unresectable or metastatic melanoma in adults and pediatric patients (≥ 12 years).
2) Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of > 1 mm who have undergone complete resection, including total lymphadenectomy.
3) In combination with Opdivo® (nivolumab for intravenous injection) for the treatment of patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma (RCC).
4) In combination with Opdivo for the treatment of adult and pediatric patients ≥ 12 years of age with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal

cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.[1]

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, and non-small cell lung cancer (NSCLC).[2] The indication for NSCLC is not addressed below since it is for activity against tumor mutational burden (TMB) in combination with Opdivo. The NCCN NSCLC guidelines note TMB as an evolving biomarker that may be helpful in selecting patients for immunotherapy.[3] There is no consensus on how to measure TMB.

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

20. 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)** The patient is 12 years of age or greater; AND
- **B)** The patient meets ONE of the following criteria (i or ii):
  - **i.** The patient has tried chemotherapy.
    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]); OR
  - **ii.** The 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.

21. 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)** The patient is 12 years of age or greater; AND
- **B)** The 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.
    Note: For example, in patients with cutaneous melanoma who have undergone complete resection, including total lymphadenectomy; AND
- **C**) The medication is prescribed by or in consultation with an oncologist.

22. Renal Cell Carcinoma. Approve for 4 months if the patient meets the following criteria (A, B, and C):
- **K)** The 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
- **M)** The medication is prescribed by or in consultation with an oncologist.

Other Uses with Supportive Evidence

4. Small Cell Lung Cancer. Approve for 1 year if the patient meets all of the following (A, B, and C):
- **C)** The patient has tried at least one other systemic chemotherapy regimen within the past 6 months.
  Note: Examples of chemotherapy are cisplatin and etoposide, carboplatin and etoposide; AND
- **D)** 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.

5. Malignant Pleural Mesothelioma. Approve for 1 year if the patient meets the following (A, B, and C):
A) The patient has tried at least one other chemotherapy regimen.
Note: Examples of chemotherapy are cisplatin, gemcitabine, Alimta (pemetrexed for injection), carboplatin, bevacizumab; AND
B) 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.

6. Small Bowel Adenocarcinoma, Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR). Approve for 1 year if the patient meets the following (A, B, and C):
A) The patient has advanced or metastatic disease; AND
B) 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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Yervoy 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.

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

376. Yervoy® Intravenous Infusion [prescribing information]. Bridgewater, NJ: Sanofi-Aventis; May 2019.
377. The NCCN Drugs and Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 20, 2019. Search term: ipilimumab.
378. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 7.2019). 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 23, 2019.

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

33. 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.

187. Re-treatment with Yescarta. Yescarta is for one time use, repeat dosing is not approvable.

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

704. Yescarta™ suspension for intravenous infusion [prescribing information]. Santa Monica, CA: Kite Pharma; May 2019.
705. 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.
706. 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.
707. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Injectable) – Zaltrap® (ziv-aflibercept injection for intravenous infusion – Regeneron Pharmaceuticals, Inc./Sanofi-Aventis)

REVIEW DATE: 09/25/2019

OVERVIEW

Zaltrap is a recombinant fusion protein consisting of vascular endothelial growth factor (VEGF) receptors 1 and 2 fused to the Fc portion of the human immunoglobulin G1 (IgG1).[1] Zaltrap acts as a soluble receptor that binds to human VEGF-A, VEGF-B, and placental growth factor (PIGF). By binding to these endogenous ligands, Zaltrap can inhibit the binding and activation of their cognate receptors, resulting in decreased neovascularization and decreased vascular permeability.

Zaltrap, 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 2.2019 – May 15, 2019)[2] and rectal cancer guidelines (version 2.2019 – May 15, 2019)[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 should not be used as adjuvant therapy for patients with Stage III or IV colon cancer outside of a clinical trial.

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 Avastin 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

225. Colon and Rectal Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):

- **47.** Zaltrap is prescribed by or in consultation with an oncologist; AND
- **48.** The patient has advanced or metastatic disease; AND
- **49.** Patient has been previously treated with an oxaliplatin- or fluoropyrimidine-containing regimen. (Note: Fluoropyrimidines include 5-fluorouracil [5-FU], capecitabine); AND
- **50.** The patient has not previously been treated with FOLFIRI. (Note: FOLFIRI includes 5-fluorouracil [5-FU], leucovorin, and irinotecan); AND
- **51.** Zaltrap will be used in combination with 5-fluorouracil (5-FU) or capecitabine and/or irinotecan.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Zaltrap 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.

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
708. Zaltrap® injection for intravenous infusion [prescribing information]. Bridgewater, NJ: Regeneron Pharmaceutical, Inc./sanofi-aventis U.S. LLC; June 2016.
709. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 2.2019 – May 15, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 4, 2019.
710. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (Version 2.2019 – May 15, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 4, 2019.
711. The NCCN Drugs and Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 4, 2019. Search term: ziv-aflibercept.

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

226. 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:

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

712. Zepzelca injection for intravenous use [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals; June 2020.
713. 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.
714. 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.

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

227. 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.

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

715. Jelmyto™ for pyelocalyceal solution [prescribing information]. Princeton, NJ: UroGen Pharma; April 2020.
716. 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.
717. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Other) – Valrubicin solution for intravesical use (Valstar – Endo Pharmaceuticals Solution, generics)

REVIEW DATE: 10/16/2019

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 4.2019 – July 10, 2019) 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

228. Bladder Cancer. Approve for 2 months if the patient meets the following criteria (A, B, and C):

- **A)** The patient is ≥ 18 years of age; AND
- **B)** The patient meets one of the following (i or ii):
  - **i.** The 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)** Valrubicin is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Valrubicin 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.

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

718. Valstar solution [prescribing information]. Malvern, PA: Endo Pharmaceuticals Solutions; April 2016.
719. The NCCN Drugs and Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 25, 2019. Search term: valrubicin.
720. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (Version 4.2019 – July 10, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 25, 2019.

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:

193. **Concomitant use with Xiidra™ (lifitegrast ophthalmic solution).** There are no data to support the concomitant use of Restasis or Cequa and Xiidra.

194. **Concomitant use of Cyclosporine Products.** There is no evidence to support additive efficacy of combining Restasis and Cequa.

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

379. Restasis® ophthalmic emulsion 0.05% [prescribing information]. Irvine, CA: Allergan, Inc.; July 2017.
380. Restasis Multidose™ ophthalmic emulsion 0.05% [prescribing information]. Irvine, CA: Allergan; July 2017.
381. Cequa™ ophthalmic solution [prescribing information]. Cranbury, NJ: Sun Pharmaceutical Industries; August 2018.
382. Data on file. Cequa® Product Dossier. Based on AMCP guidelines for formulary submission. Sun Pharmaceutical Industries, Inc.; August 2018.
383. 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.
384. Yagci A, Gurdal C. The role and treatment of inflammation in dry eye disease. *Int Ophthalmol*. 2014;34(6):1291-1301.
385. Ramos-Casals M, Tzioufas AG, Stone JH, et al. Treatment of primary Sjogren syndrome – a systematic review. *JAMA*. 2010;304:452-460.
386. Utine CA, Stern M, Akpek EK. Clinical review: Topical ophthalmic use of cyclosporine A. *Ocul Immunol Inflamm*. 2010;18:352-361.
387. Hessen M, Akpek EK. Ocular graft-versus-host disease. *Curr Opin Allergy Clin Immunol*. 2012;12:540-547.
388. Van Zuuren EJ, Fedorowicz Z, Carter B, et al. Interventions for rosacea (review). The Cochrane Collaboration®. *Cochrane Database Syst Rev*. 2015;4:CD003262.
389. Arman A, Demirseren DD, Takmaz T. Treatment of ocular rosacea: comparative study of topical cyclosporine and oral doxycycline. *Int J Ophthalmol*. 2015;8(3):544-549.
390. Donnenfeld E, Pflugfelder SC. Topical ophthalmic cyclosporine: pharmacology and clinical uses. *Surv Ophthalmol*. 2009;54:321-338.
391. American Academy of Ophthalmology cornea/external disease panel. Preferred practice pattern® guidelines. Blepharitis. San Francisco, CA: American Academy of Ophthalmology; 2018. Available at: www.aao.org/ppp. Accessed on August 11, 2020.
392. American Academy of Ophthalmology cornea/external disease panel. Preferred practice pattern® guidelines. Conjunctivitis. San Francisco, CA: American Academy of Ophthalmology; 2018. Available at: www.aao.org/ppp. Accessed on August 11, 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

145. 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:

196. Concomitant use with an ophthalmic cyclosporine product (Restasis®, Cequa™). There are no data to support the concomitant use of Restasis or Cequa and Xiidra.

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

393. Xiidra™ ophthalmic solution [prescribing information]. East Hanover, NJ: Novartis; July 2020.
394. 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.

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)

REVIEW DATE: 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

38. **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.)

91. **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.

92. 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.
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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)

REVIEW DATE: 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.)

198. 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.

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

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PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Luxturna™ (voretigene neparvovec-rzyl intraocular suspension for subretinal injection – Spark Therapeutics)

REVIEW DATE: 02/19/2020

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 (AAV2) which has been genetically modified to express the human RPE65 gene. 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.

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. Luxturna is available as a single-dose vial containing 0.5 mL (extractable volume) of a 5×10^{12} vg/mL concentration of Luxturna, which requires a 1:10 dilution prior to administration with the supplied diluent.

Disease Overview

Inherited retinal dystrophies (IRDs) 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 blocks the visual cycle. This 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 deficiency in the RPE65 protein mainly affects rod photoreceptors that mediate peripheral vision and night vision.[3] 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. Injection of Luxturna into the subretinal space results in transduction of some retinal pigment epithelial cells with a complementary deoxyribonucleic acid (cDNA) encoding normal human RPE65 protein, thereby providing the potential to restore the visual cycle.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Luxturna. Because of the 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 or in consultation with a physician who specializes in the condition being treated. All approvals are provided for one injection per eye. Note that 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, and D):
   - **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
Luxturna 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.)

93. 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.

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
313. Luxturna™ subretinal injection [prescribing information]. Philadelphia, PA: Spark Therapeutics, Inc.; December 2019.
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PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Oxervate™ (cenegermin-bkbj ophthalmic solution – Dompé farmaceutici S.p.A)

REVIEW DATE: 11/06/2019

OVERVIEW

Oxervate, a recombinant human nerve growth factor, is indicated for the treatment of neurotrophic keratitis.[1] Oxervate was designated as a Breakthrough Therapy and an Orphan Drug by the FDA.[2,3]

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.[2,4,5] 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.[6,7] 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.[4,7]

Guidelines/Recommendations

Prior to the approval of Oxervate, there are 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.[6] 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.[4,5] 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.[7] Surgical interventions are reserved for refractory cases.[4,5,7]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Oxervate. 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. All approvals are provided for 1 year in duration unless otherwise noted below.

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

Oxervate 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.)

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

405. Oxervate™ ophthalmic solution [prescribing information]. L'Aquila, Italy: Domp farmaceutici S.p.A; January 2019.
406. Oxervate. FDA Clinical Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761094Orig1s000TOC.cfm. Accessed on October 31, 2019.
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PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Tepezza™ (teprotumumab injection for intravenous use – Horizon Therapeutics)

REVIEW DATE: 01/29/2020

OVERVIEW

Tepezza, an insulin-like growth factor-1 receptor (IGF-1R) antagonist antibody, is indicated for the treatment of patients with thyroid eye disease (TED).[1] The safety and efficacy have not been established in patients who are pregnant or pediatric patients. Tepezza is a fully human immunoglobulin G monoclonal antibody that binds IGF-1R, a tyrosine kinase cell surface receptor that is overexpressed in the orbital fibroblasts of TED patients.[2,3] Tepezza targets and binds to IGF-1R, inhibits IGF-1R autophosphorylation, decreases cell surface expression of IGF-1R and prevents downstream signaling. Based on the mechanism of action, Tepezza is theorized to decrease inflammation and tissue growth, thus reducing the signs and symptoms of TED. 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.

Disease Overview

TED is a progressive, vision-threatening autoimmune inflammatory disease of the eye and orbital tissues with predominant features of fibrosis and adipogenesis.[4] It is also recognized in literature as Graves' ophthalmopathy, Graves' orbitopathy, thyroid-associated ophthalmopathy, and thyroid orbitopathy. TED 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).[5] Orbital fibroblasts appear responsible for soft tissue enlargement by expressing potential pathogenic autoantigens, such as thyrotropin receptor and IGF-1R.[6] 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.

POLICY STATEMENT

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

229. Thyroid Eye Disease. (Note: Thyroid Eye Disease is also recognized as Graves' ophthalmopathy, Graves' orbitopathy, thyroid-associated ophthalmopathy, and thyroid orbitopathy.) 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) According to the prescriber, the 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.); AND

C) Teppeza is prescribed by or in consultation with an ophthalmologist, endocrinologist, or a physician who specializes in thyroid eye disease.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Tepezza 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.)

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

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726. Shan S, Douglas R. The pathophysiology of thyroid eye disease. J Neuroophthalmol. 2014 Jun;34(2):177-85.

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:

201. Blepharoptosis. Due to insufficient clinical efficacy data, approval is not recommended for Upneeq.

202. 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%).

203. 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.

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

727. Upneeq™ ophthalmic solution [prescribing information]. Bridgewater, NJ: Osmotica/RVL Pharmaceuticals; July 2020.
728. 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.
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731. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Beovu® (brolucizumab intravitreal injection – Novartis)

REVIEW DATE: 10/23/2019

OVERVIEW

Beovu, a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD).[1] The recommended dose for Beovu is 6 mg administered by intravitreal (IVT) injection every monthly (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. Because of the specialized skills required for evaluation and diagnosis, the injection technique required, and the monitoring required for adverse events and long-term efficacy, approval requires Beovu to be prescribed by or in consultation with an ophthalmologist. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Beovu is recommended in those who meet the following criteria.

FDA-Approved Indications

230. 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

231. 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

Beovu 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.)

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

732. Beovu® [prescribing information]. Hanover, NJ: Novartis Pharmaceuticals; October 2019.
733. Barakat MR, Kaiser PK. VEGF inhibitors for the treatment of neovascular age-related macular degeneration. *Expert Opin Investig Drugs*. 2009;18(5):637-646.
734. Tolentino M. Systemic and ocular safety of intravitreal anti-VEGF therapies for ocular neovascular disease. *Surv Ophthalmol*. 2011;56(2):95-113.
735. Kinnunen K, Ylä-Herttuala S. Vascular endothelial growth factors in retinal and choroidal neovascular diseases. *Ann Med*. 2012;44(1):1-17.
736. Horsley MB, Kahook MY. Anti-VEGF therapy for glaucoma. *Curr Opin Ophthalmol*. 2010;21(2):112-117.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
New Policy	--	10/23/2019

* 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: Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Eylea® (aflibercept intravitreal injection – Regeneron)

REVIEW DATE DATE: 11/06/2019

OVERVIEW

Eylea, a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the treatment of neovascular (wet) age-related macular degeneration, macular edema following retinal vein occlusion, diabetic macular edema, and diabetic retinopathy.[1] 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. Because of the specialized skills required for evaluation and diagnosis, the injection technique required, and the monitoring required for adverse events and long-term efficacy, approval requires Eylea to be prescribed by or in consultation with an ophthalmologist. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Eylea is recommended in those who meet the following criteria.

FDA-Approved Indications

232. Neovascular (Wet) Age-Related Macular Degeneration. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

233. Macular Edema Following Retinal Vein Occlusion. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

3. Diabetic Macular Edema. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

4. Diabetic Retinopathy. 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

Eylea 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.)

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
737. Eylea® injection [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; May 2019.
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PRIOR AUTHORIZATION POLICY (DRAFT)

POLICY: Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Lucentis® (ranibizumab intravitreal injection – Genentech)

REVIEW DATE: 11/06/2019

OVERVIEW
Lucentis, a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO), diabetic macular edema (DME), diabetic retinopathy (DR), and myopic choroidal neovascularization (mCNV).[1] 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. Because of the specialized skills required for evaluation and diagnosis, the injection technique required, and the monitoring required for adverse events and long-term efficacy, approval requires Lucentis to be prescribed by or in consultation with an ophthalmologist. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Lucentis is recommended in those who meet the following criteria.

FDA-Approved Indications

234. Neovascular (Wet) Age-Related Macular Degeneration. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

235. Macular Edema Following Retinal Vein Occlusion. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

5. Diabetic Macular Edema. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

6. Diabetic Retinopathy. Approve for 1 year if administered by or under the supervision of an ophthalmologist.

7. Myopic Choroidal Neovascularization. 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

Lucentis 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.)

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

742. Lucentis® intravitreal injection [prescribing information]. South San Francisco, CA: Genentech, Inc.; April 2017.
743. Barakat MR, Kaiser PK. VEGF inhibitors for the treatment of neovascular age-related macular degeneration. *Expert Opin Investig Drugs*. 2009;18(5):637-646.
744. Tolentino M. Systemic and ocular safety of intravitreal anti-VEGF therapies for ocular neovascular disease. *Surv Ophthalmol*. 2011;56(2):95-113.
745. Kinnunen K, Ylä-Herttuala S. Vascular endothelial growth factors in retinal and choroidal neovascular diseases. *Ann Med*. 2012;44(1):1-17.
746. Horsley MB, Kahook MY. Anti-VEGF therapy for glaucoma. *Curr Opin Ophthalmol*. 2010;21(2):112-117.

PRIOR AUTHORIZATION POLICY

POLICY: Ophthalmology – Vascular Endothelial Growth Factor Inhibitors – Macugen® (pegaptanib sodium intravitreal injection – Valeant)

REVIEW DATE: 11/06/2019

OVERVIEW

Macugen, a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the treatment of neovascular (wet) age-related macular degeneration.[1] The recommended dose for Macugen is 0.3 mg administered by intravitreal injection once every 6 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 Macugen. Because of the specialized skills required for evaluation and diagnosis, the injection technique required, and the monitoring required for adverse events and long-term efficacy, approval requires Macugen to be prescribed by or in consultation with an ophthalmologist. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Macugen is recommended in those who meet the following criteria.

FDA-Approved Indications

236. 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

7. **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

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

REFERENCES

747. Macugen® injection [prescribing information]. Cedar Knolls, NJ: Eyetech Inc.; October 2011.
748. Barakat MR, Kaiser PK. VEGF inhibitors for the treatment of neovascular age-related macular degeneration. *Expert Opin Investig Drugs.* 2009;18(5):637-646.
749. Tolentino M. Systemic and ocular safety of intravitreal anti-VEGF therapies for ocular neovascular disease. *Surv Ophthalmol*. 2011;56(2):95-113.
750. Kinnunen K, Ylä-Herttuala S. Vascular endothelial growth factors in retinal and choroidal neovascular diseases. *Ann Med*. 2012;44(1):1-17.
751. Horsley MB, Kahook MY. Anti-VEGF therapy for glaucoma. *Curr Opin Ophthalmol*. 2010;21(2):112-117.

PRIOR AUTHORIZATION POLICY

POLICY: Opioids – Fentanyl Transmucosal Drugs

- 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: 10/23/2019

OVERVIEW

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] The transmucosal fentanyl products 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] 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 products 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 products 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-9/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:

Food and Drug Administration (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,[7] or uncontrollable nausea/vomiting (In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion); OR
     - **ii.** Patient is unable to take two other short-acting narcotics (e.g., oxycodone, morphine sulfate, hydromorphone, etc.) secondary to allergy or severe adverse events (In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion); AND
   - **B)** Patient is on or will be on an oral or transdermal long-acting narcotic (e.g., Duragesic, OxyContin, morphine extended-release), or the patient is on intravenous, subcutaneous, or spinal (intrathecal, epidural) narcotics (e.g., morphine sulfate, hydromorphone, fentanyl citrate).

   Actiq (generics), Abstral, Fentora, Lazanda, and Subsys are indicated 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]

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Fentanyl transmucosal drugs 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. **Acute and/or Postoperative Pain** including 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.[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.[8] 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. Shaiova L, Lapin J, Manco LS, et al. Tolerability and effects of two formulations of oral transmucosal fentanyl citrate (OTFC; ACTIQ) in patients with radiation-induced oral mucositis. *Support Care Cancer*. 2004;12:268-273.
8. Landy SH. Oral transmucosal fentanyl citrate for the treatment of migraine headache pain in outpatients: a case series. *Headache.* 2004;44(8):762-766.

APPENDIX A

STC*	STC Description
0475	ANTINEOPLASTICS, MISCELLANEOUS
7235	ANTINEOPLASTICS ANTIBODY/ANTIBODY-DRUG COMPLEXES
0471	ANTINEOPLASTIC - ANTIMETABOLITES
C232	ANTINEOPLASTIC - MTOR KINASE INHIBITORS
9150	ANTINEOPLASTIC SYSTEMIC ENZYME INHIBITORS
0470	ANTINEOPLASTIC - ALKYLATING AGENTS
C593	ANTINEOPLASTIC - AROMATASE INHIBITORS
8585	ANTINEOPLAST HUM VEGF INHIBITOR RECOMB MC ANTIBODY
B759	ANTINEOPLAST, HISTONE DEACETYLASE (HDAC) INHIBITORS
6323	ANTINEOPLASTIC - ANTIANDROGENIC AGENTS
C532	ANTINEOPLASTIC - TOPOISOMERASE I INHIBITORS
G575	ANTINEOPLASTIC - MEK1 AND MEK2 KINASE INHIBITORS
F501	ANTINEOPLASTIC - VEGFR ANTAGONIST
G590	ANTINEOPLASTIC - ANTI-CD38 MONOCLONAL ANTIBODY
8254	ANTINEOPLASTIC LHRH(GNRH) AGONIST, PITUITARY SUPPR.
G607	ANTINEOPLASTIC - ANTI-SLAMF7 MONOCLONAL ANTIBODY
8569	ANTINEOPLASTIC EGF RECEPTOR BLOCKER MCLON ANTIBODY
E150	ANTINEOPLASTIC - HEDGEHOG PATHWAY INHIBITOR
8460	ANTINEOPLASTIC LHRH(GNRH) ANTAGONIST,PITUIT.SUPPRS
D560	ANTINEOPLASTIC - HALICHONDRIN B ANALOGS
G545	ANTINEOPLASTIC - IMMUNOTHERAPY, VIRUS-BASED AGENTS
C370	ANTINEOPLASTIC - EPOTHILONES AND ANALOGS
E039	ANTINEOPLASTIC - JANUS KINASE (JAK) INHIBITORS
F665	ANTINEOPLASTIC, ANTI-PROGRAMMED DEATH-1 (PD-1) MAB
H018	ANTINEOPLASTIC, PDGFR-ALPHA BLOCKER MC ANTIBODY
0472	ANTINEOPLASTIC - VINCA ALKALOIDS
7977	ANTINEOPLASTIC IMMUNOMODULATOR AGENTS
D426	ANTINEOPLASTIC - IMMUNOTHERAPY, THERAPEUTIC VAC
F495	ANTINEOPLASTIC - INTERLEUKIN-6(IL-6)INHIB,ANTIBODY
G802	ANTINEOPLASTIC- B CELL LYMPHOMA-2(BCL-2) INHIBITORS
E600	ANTINEOPLASTIC - VEGF-A,B AND PLGF INHIBITORS
0473	ANTIBIOTIC ANTINEOPLASTICS
D687	CYTOTOXIC T-LYMPHOCYTE ANTIGEN (CTLA-4) RMC ANTIBODY
G857	ANTI-PROGRAMMED CELL DEATH-LIGAND 1 (PD-L1) MAB
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

* Excluding topical products

APPENDIX B

ICD-9 Codes	ICD-10 Codes
Cancer-related codes	
140.* to 209	C00.* to D09.*
230.* to 234	D3A.* to D48.*
235.* to 239	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

106. 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.)

95. 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]

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

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317. Nucynta® ER extended-release oral tablets [prescribing information]. Stoughton, MA: Collegium Pharmaceutical, Inc.; October 2019.
318. Embeda® extended-release capsules [prescribing information]. New York, NY: Pfizer Inc.; October 2019.
319. Kadian® capsules [prescribing information]. Madison, NJ: Allergan USA, Inc.; October 2019.
320. Avinza® capsules [prescribing information]. New York, NY: Pfizer Inc.; May 2014.
321. MS Contin® tablets [prescribing information]. Stamford, CT: Purdue Pharma L.P.; October 2019.
322. OxyContin® tablets [prescribing information]. Stamford, CT: Purdue Pharma LP; October 2019.
323. 9. Oxymorphone ER tablets [prescribing information]. Bridgewater, NJ: Amneal Pharmaceuticals LLC; June 2019.
324. Exalgo® extended-release tablets [prescribing information]. Webster Groves, MO: SpecGx LLC; October 2019.
325. Zohydro® ER extended-release capsules [prescribing information]. Morristown, NJ: Currax Pharmaceuticals LLC; October 2019.
326. Hysingla™ ER extended-release tablets [prescribing information]. Stamford, CT: Purdue Pharma L.P.; October 2019.
327. Xtampza ER® extended-release capsules [prescribing information]. Cincinnati, OH: Patheon Pharmaceuticals; October 2019.
328. Arymo® ER extended-release tablets [prescribing information]. Wayne, PA: Egalet US Inc.; October 2019.

329. Conzip® extended-release capsules [prescribing information]. Bridgewater, NJ: Vertical Pharmaceuticals, LLC; October 2019.
330. Belbuca® buccal film [prescribing information]. Raleigh, NC: BioDelivery Sciences International, Inc.; October 2019.
331. Duragesic® transdermal system [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; October 2019.
332. Dolophine® [prescribing information]. Eatontown, NJ: West-Ward Pharmaceuticals Corp.; October 2019.
333. Dixon DW, Peirson RP. Opioid abuse. Page last updated: March 23, 2020. Available at: http://emedicine.medscape.com/article/287790-overview#showall . Accessed on April 24, 2020.
334. Substance Abuse and Mental Health Services Administration. (2017). Key substance use and mental health indicators in the United States: results from the 2016 National Survey on Drug Use and Health (HHS Publication No. SMA 17-5044, NSDUH Series H-52). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Available at: http://www.samhsa.gov/data/. Accessed on April 24, 2020.
335. 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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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

107. 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:

97. 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]

98. 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. Ultram® ER [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals Inc.; August 2017.
2. Conzip® [prescribing information]. Bridgewater, NJ: Vertical Pharmaceuticals, Inc.; October 2019.
3. Tramadol Hydrochloride Extended-Release Capsules [prescribing information]. Bridgewater, NJ: Trigen Laboratories, LLC; October 2019.
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.

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
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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
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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 – Apokyn Prior Authorization Policy

- Apokyn® (apomorphine hydrochloride for subcutaneous injection)

REVIEW DATE: 08/19/2020

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

108. Parkinson's Disease. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):

i. Patient is diagnosed with advanced Parkinson's disease; AND

ii. Patient is experiencing "off" episodes such as muscle stiffness, slow movements, or difficulty starting movements; AND

iii. Patient is currently receiving carbidopa/levodopa therapy; AND

iv. 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).

E) 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:

209. 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]

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

752. Apokyn® subcutaneous injection [prescribing information] Louisville, KY: US WorldMeds; April 2020.
753. 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.

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

237. 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:

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

754. Duopa™ [prescribing information] Bridgewater, NJ: Valeant Pharmaceuticals; May 2020.

755. 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.
756. 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.

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

238. 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:

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

REFERENCES

757. Inbrija™ powder for inhalation [prescribing information]. Ardsley, NY: Acorda Therapeutics, Inc.; September 2019.
758. 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.

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

239. 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.

240. 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.

241. 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:

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
759. Lodosyn® [prescribing information] Bridgewater, NJ: Aton Pharma; February 2017.

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

242. 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:

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

760. Nourianz™ [prescribing information]. Bedminster, NJ: Kyowa Kirin, Inc.; May 2020.
761. 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.

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

146. Parkinson's Disease Psychosis. Approve for 1 year if the patient meets all of the following criteria (A, B, and C):
- **1.** Patient has hallucinations and delusions associated with Parkinson's disease pychosis; AND
- **2.** Patient does not have dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis; AND
- **3.** 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:

215. 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.

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

762. Nuplazid® tablets and capsules [prescribing information]. San Diego, CA: Acadia Pharmaceuticals Inc.; May 2019.

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

243. 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:

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

REFERENCES

763. Tasmar® oral tablets [prescribing information] Bridgewater, NJ: Valeant Pharmaceuticals; December 2018.

764. 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.

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

244. 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:

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
765. Zelapar® orally disintegrating tablets [prescribing information] Bridgewater, NJ: Valeant Pharmaceuticals; February 2020.
766. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Parkinson's Disease – Amantadine Extended-Release Drugs
- Gocovri™ (amantadine extended-release capsules – Adamas Pharma)
- Osmolex ER™ (amantadine extended-release tablets – Vertical Pharmaceuticals)

DATE REVIEWED: 12/18/2019

OVERVIEW
Gocovri is indicated for the treatment of dyskinesia in patients with Parkinson's disease (PD) receiving levodopa-based therapy, with or without concomitant dopaminergic medications.[1] The initial daily dosage of Gocovri is 137 mg once daily (QD) at bedtime. After one week, increase to the recommended dosage of 274 mg (equivalent to 340 mg amantadine hydrochloride) QD at bedtime. Gocovri is available in 68.5 mg and 137 mg strengths (as 85 mg or 170 mg amantadine hydrochloride, respectively).

Osmolex ER is indicated for the treatment of Parkinson's disease and for the treatment of drug-induced extrapyramidal reactions in adult patients.[2] The recommended initial dosage of Osmolex ER is 129 mg QD in the morning. The dosage may be increased in weekly intervals to a maximum daily dose of 322 mg (administered as a 129 mg and 193 mg tablet), taken in the morning. For patients unable to tolerate more than 100 mg/day of immediate-release (IR) amantadine, there is no equivalent dose or dosing regimen of Osmolex ER. Osmolex ER is available in 129 mg, 193 mg, and 258 mg strengths (as 160 mg, 240 mg, or 320 mg amantadine hydrochloride, respectively).

Amantadine hydrochloride is available as an IR 100 mg capsule, 100 mg tablet, and 50 mg/5 mL oral solution. The amantadine IR products are indicated for the prophylaxis and treatment of signs and symptoms of infection caused by various strains of influenza A virus; idiopathic PD [Paralysis Agitans], postencephalitic 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.[3-5] For the treatment of PD, the usual dose of amantadine IR is 100 mg twice daily (BID) when used alone. An initial dose of amantadine IR is 100 mg daily for patients with serious associated medical illnesses or who are receiving

high doses of other antiparkinson drugs; the dose may be increased to 100 mg BID, if necessary. Patients initially deriving benefit from amantadine may experience a fall-off of effectiveness after a few months; benefit may be regained by increasing the dose to 300 mg/day in divided doses. Occasionally, patients whose responses are not optimal with amantadine IR 200 mg daily may benefit from an increase up to 400 mg/day in divided doses. For the treatment of drug-induced extrapyramidal reactions, the usual dose of amantadine IR is 100 mg BID. Occasionally, patients whose responses are not optimal with amantadine IR 200 mg/day may benefit from an increase up to 300 mg/day in divided doses.

Disease Overview

PD is a common neurodegenerative disease and is a chronic, progressive disorder of the extrapyramidal nervous system affecting the mobility and control of the skeletal muscular system.[6,7] Approximately 50,000 Americans are diagnosed each year with PD and it is estimated that 1 million people in the US have the condition. PD typically affects patients who are greater than 60 years of age.[8] Its characteristic features include resting tremor, rigidity, bradykinetic movements, and postural instability.[6,7] As these symptoms become more pronounced, patients with PD may have difficulty walking, talking, or completing other simple tasks. Early symptoms of PD are subtle and occur gradually. The disease course varies considerably as well as the intensity of symptoms. While some patients become severely disabled, others experience only minor motor disruptions. Resting tremor is the major symptom for some individuals, while for others tremor is only a minor complaint and other manifestations may be more troublesome. It is not possible to predict which symptoms will affect an individual. PD symptoms are thought to be related to depletion of dopamine in the corpus striatum. Use of dopamine is ineffective in the treatment of PD because it does not penetrate the blood-brain barrier. However, levodopa, the metabolic precursor of dopamine, does cross the blood-brain barrier and is believed to be converted to dopamine in the brain. This is thought to be the mechanism whereby levodopa relieves PD symptoms. Other medications are also utilized to improve mobility.

Although initially effective, dopaminergic therapies are eventually complicated by motor fluctuations, including “off” time (periods during which PD symptoms return when the medication effect wears off) and dyskinesia (drug-induced involuntary movements, e.g., chorea and dystonia) in most patients.[9] These motor complications can impair patient quality of life and cause substantial disability. Risk factors for motor complications include younger age at the onset of PD, increased disease severity, higher levodopa dosage, and longer disease duration. These problems are often addressed with levodopa adjustments and the addition of adjunctive medications. According to a review of the treatment of motor symptoms in advanced PD, amantadine is currently the most effective medication approved for the treatment of levodopa-induced dyskinesias.[10]

Clinical Efficacy

Gocovri was assessed in two randomized, double-blind, placebo-controlled efficacy trials, EASE LID (n = 121) and EASE LID 3 (n = 75), in patients with PD and dyskinesia.[1] In both studies, the primary efficacy endpoint was the change in total score of the Unified Dyskinesia Rating Scale (UDysRS) between baseline and Week 12. Patients in EASE LID and EASE LID 3 were treated with a stable dose of levodopa, with 32% of patients on levodopa monotherapy; 54% of patients and 44% of patients were treated with concomitant dopamine agonists and/or MAO-B inhibitors, respectively. In EASE LID and EASE LID 3, a significant decrease in mean UDysRS total score (reduction in dyskinesia) was observed at Week 12 in patients treated with Gocovri compared with placebo (EASE LID treatment difference: -7.9; $P = 0.0009$ and EASE LID 3 treatment difference: -14.4; $P < 0.0001$). Gocovri has not been compared with amantadine IR or other active treatments in clinical trials.

No clinical efficacy studies were undertaken for approval of Osmolex ER.[2] The efficacy of Osmolex ER is based upon bioavailability studies comparing Osmolex ER with IR amantadine.

Guidelines

The 2006 American Academy of Neurology (AAN) guideline on the treatment of PD with motor fluctuations and dyskinesia recommends considering the use of amantadine in patients with PD and motor fluctuations to reduce dyskinesia (Level C).[9] The authors concluded that amantadine IR (given as 100 mg BID) is possibly effective in reducing dyskinesia based on one Class II study. The guidelines have not been updated to include Gocovri or Osmolex ER.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of amantadine extended-release products. Because of the specialized skills required for evaluation and diagnosis of patients treated with amantadine extended-release as well as the monitoring required for adverse events and long-term efficacy, initial approval requires amantadine extended-release to be prescribed by or in consultation with a physician who specializes in patients with PD. 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

I. Coverage of Gocovri is recommended in those who meet the following criteria:

FDA-Approved Indications

147. Dyskinesia in Parkinson's Disease (PD). Approve for the duration noted below if patient meets ONE of the following (A or B):

A) Initial Therapy. Approve Gocovri for 3 months if the patient meets the following criteria (i, ii, and iii):
- **i.** Gocovri is prescribed by or in consultation with a neurologist; AND
- **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 IR 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.

B) Patients Currently Receiving Gocovri. Approve Gocovri for 1 year if the patient meets the following criteria (i, ii, iii, and iv):
- **i.** Gocovri is prescribed by or in consultation with a neurologist; AND
- **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 IR 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. Patient has had a response to therapy (e.g., decrease in dyskinesia), as determined by the prescriber.

II. Coverage of Osmolex ER is recommended in those who meet the following criteria:

FDA-Approved Indications

1. Parkinson's Disease (PD). Approve for the duration noted below if patient meets ONE of the following (A or B):

A) Initial Therapy. Approve Osmolex ER for 3 months if the patient meets the following criteria (i and ii):

i. Osmolex ER is prescribed by or in consultation with a neurologist; 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 IR 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.

B) Patients Currently Receiving Osmolex ER. Approve Osmolex ER for 1 year if the patient meets the following criteria (I, ii, and iii):

i. Osmolex ER is prescribed by or in consultation with a neurologist; 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 IR 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), as determined by the prescriber.

148. Drug-Induced Extrapyramidal Reactions. Approve for the duration noted below if patient meets ONE of the following (A or B):

A) Initial Therapy. Approve Osmolex ER for 3 months if the patient meets the following criteria (i and ii):

i. Osmolex ER is prescribed by or in consultation with a neurologist; 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 IR 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.

B) Patients Currently Receiving Osmolex ER. Approve Osmolex ER for 1 year if the patient meets the following criteria (i, ii, and iii):

i. Osmolex ER is prescribed by or in consultation with a neurologist; 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 IR 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 extrapyramidal reactions), as determined by the prescriber.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Amantadine extended-release 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. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

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

REFERENCES

336. Gocovri™ extended-release capsules [prescribing information]. Emeryville, CA: Adamas Pharma LLC; August 2017.
337. Osmolex ER™ extended-release tablets [prescribing information]. Bridgewater, NJ: Vertical Pharmaceuticals, LLC.; February 2018.
338. Amantadine capsules [prescribing information]. Bridgewater, NJ: Alembic Pharmaceuticals, Inc.; April 2017.
339. Amantadine tablets [prescribing information]. Sunrise, FL: Cipla USA, Inc.; March 2019.
340. Amantadine oral solution [prescribing information]. Amityville, NY: Hi-Tech Pharmacal Co., Inc.; July 2016.
341. Connolly BS, Lang AE. Pharmacological treatment of Parkinson disease. A review. *JAMA*. 2014;311(16):1670-1683.
342. National Institute of Neurological Disorders and Stroke (NINDS) Parkinson's disease information page. Updated on: August 28, 2019. Available at: https://www.ninds.nih.gov/Disorders/All-Disorders/Parkinsons-Disease-Information-Page. Accessed on December 3, 2019.
343. FDA News Release. FDA approves drug to treat Parkinson's disease. March 21, 2017. Available at: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm547852.htm. Accessed on December 3, 2019.
344. 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(7):983-995.
345. Moore H, Shpiner DS, Luca CC. Management of Motor Features in Advanced Parkinson Disease. *Clin Geriatr Med*. 2020;36:43-52.

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

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

245. Parkinson's Disease. Approve for 1 year if patient meets all of 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 is currently receiving carbidopa/levodopa therapy; AND
- **D)** 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.
- **E)** 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:

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

767. Kynmobi™ sublingual film [prescribing information]. Marlborough, MA: Sunovion Pharmaceuticals; May 2020.
768. 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.

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

246. 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:

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
769. Ongentys® capsules [prescribing information]. San Diego, CA: Neurocrine Biosciences; May 2020.
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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)

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.

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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.)

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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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.)

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

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PRIOR AUTHORIZATION POLICY

POLICY: Pheochromocytoma

- Demser® (metyrosine capsules – Pharmaceutics International/Valeant/Aton Pharma)
- Phenoxybenzamine capsules (Dibenzyline® – Concordia Pharmaceuticals, generics)

APPROVAL DATE: 08/28/2019

OVERVIEW

Demser, a tyrosine hydroxylate inhibitor, is indicated in the treatment of pheochromocytoma for: 1) preoperative preparation of patients for surgery; 2) management of patients when surgery is contraindicated; and 3) chronic treatment of patients with malignant pheochromocytoma.[1] Blocking tyrosine hydroxylase results in decreased endogenous levels of catecholamines (e.g., epinephrine, norepinephrine, and dopamine). The recommended initial dose of Desmer for adults and children aged ≥ 12 years is 250 mg four times daily. This may be increased by 250 to 500 mg every day to a maximum of 4.0 grams/day in divided doses. When used for preoperative preparation, the optimally effective dose of Demser should be administered for at least 5 to 7 days. Optimally effective dosages for Demser are usually between 2.0 and 3.0 grams/day, and the dose should be titrated by monitoring clinical symptoms and catecholamine excretion. In those who are hypotensive, the dosage should be titrated to achieve normalization of blood pressure and control of clinical symptoms. In those who are usually normotensive, the dose should be titrated to the amount that will reduce urinary metanephrines and/or vanillylmandelic acid by ≥ 50%. If patients are not adequately controlled by the use of Demser, an alpha-adrenergic blocking agent (e.g., phenoxybenazmine) should be added.

Phenoxybenzamine (Dibenzyline®, generics), 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] The dose should be adjusted to meet the needs of each patient. Small initial doses should be slowly increased until the desired effect is achieved or the adverse events (AEs) from blockage become troublesome. After each increase, the patient should be observed on that level before instituting another increase.

Disease Overview

Pheochromocytoma is a tumor that arises from adrenomedullary chromaffin cells that produce catecholamines such as epinephrine, norepinephrine, and dopamine.[3-5] Some of the tumors are malignant. This condition is uncommon and the reported prevalence is up to 0.6% of patients with general hypertension. The catecholamine secretion may cause hypertension, along with other symptoms such as diaphoresis, headache, palpitations, tachycardia, syncope, and anxiety. For some patients measures must be taken to avoid hypertensive crisis.[3-5] Some genetic syndromes associated with phenochromocytoma include multiple endocrine neoplasia type 2 (MEN2), von Hippel-Lindau syndrome, and neurofibromatosis type 1.[5] Certain foods and beverage contain tyramine which may exacerbate uncontrolled catecholamine release in patients with pheochromocytoma (e.g., chocolate, aged cheese, certain wines). Tumors may also be malignant and require surgical resection, radiation therapy, or chemotherapy.[5] Phenoxybenzamine and Demser are FDA-approved for use in pheochromocytoma.[1-2] Although not indicated, short-acting alpha adrenergic blockers (e.g., doxazosin, prazosin, and terazosin) have also been used.[5-7] Beta-blockers (e.g., atenolol, metoprolol, propranolol) are also utilized, especially in patients with tachycardia or hypertension following alpha-blockade therapy. Dihydropyridine calcium channel blockers (e.g., amlodipine, nifedipine or nicardipine) are also used for preoperative preparation as an adjunctive therapy to alpha-adrenergic blockers).[5] Although only available as an injection, phentolamine, an alpha-adrenergic blocker, is indicated for the prevention and control of hypertensive episodes that may occur in a patient with pheochromocytoma as a result of stress or manipulation during preoperative preparation and surgical excision.[8] Also, phentolamine injection is indicated for the diagnosis of pheochromocytoma by the phentolamine blocking test.

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 guidelines for Neuroendocrine and Adrenal Tumors (Version 1.2019 – March 5, 2019) address pheochromocytoma and paragangliomas.[9] 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.

Safety

Demser is associated with AEs that include severe central nervous system (CNS) changes (e.g., sedation [moderate to severe], changes in sleep pattern with medication withdrawal), extrapyramidal effects (e.g., dropping, speech difficulty, and tremor), anxiety, psychic disturbances (e.g., hallucinations, depression, confusion), diarrhea, and crystalluria. User Demser cautiously if the patient is receiving phenothiazines or haloperidol because the extrapyramidal effects of these medications may be potentiated by inhibition of catecholamine synthesis. Also, use of Demser with alcohol or other CNS depressants may increase the sedative effects. The safety and effectiveness of Demser is pediatric patients below the age of 12 years have not been established. Demser is rated in Pregnancy Category C. AEs associated with

phenoxybenzamine include those of the autonomic nervous system (e.g., postural hypotension, tachycardia, nasal congestion and miosis).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Demser and phenoxybenzamine. All approvals are provided for the duration noted below. Due to the specialized skills required for evaluation and diagnosis of patients treated with Demser and phenoxybenzamine, as well as the monitoring required for AEs and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a prescriber 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

I. Coverage of phenoxybenzamine is recommended in those who meet the following criteria:

FDA-Approved Indications

3. Pheochromocytoma. Approve phenoxybenzamine for 1 year if the patient meets the following criteria (A and B):

H) The agent is prescribed by, or in consultation with, an endocrinologist or a physician who specializes in the management of pheochromocytoma; AND

I) If brand Dibenzyline is requested, the 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]**.

II. Coverage of Demser is recommended in those who meet the following criteria:

FDA-Approved Indications

1. Pheochromocytoma.

A) Initial therapy. Approve Demser for 1 year if the patient meets all of the following criteria (i, ii, and iii):

i. The patient has tried a selective alpha blocker (e.g., doxazosin, terazosin or prazosin); AND

ii. The patient has tried phenoxybenzamine (brand or generic); AND

iii. Demser is prescribed by, or in consultation with, an endocrinologist or a physician who specializes in the management of pheochromocytoma.

B) Patient is currently receiving Demser or has received Demser in the past. Approve for 1 year if Demser is prescribed by, or in consultation with, an endocrinologist or a physician who specializes in the management of pheochromocytoma.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Demser and phenoxybenzamine 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.

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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OVERVIEW OF DISEASE STATE FOR PRIOR AUTHORIZATION DOCUMENT

Subject: Biologics for Plaque Psoriasis

Date Reviewed: December 22, 2014

Psoriasis is a multisystem disease that affects the skin and joints.[1-2] It is a chronic inflammatory skin disease with scaly, erythematous patches, papules, and plaques and is often pruritic. It affects > 3% of persons in the US (> 5 million people).[3] The disease primarily affects adults and occurs equally in men and women.[1-2] In plaque psoriasis, the most common form of psoriasis (80% to 90% of patients), there are patches of thick, inflamed skin covered with a silvery scale that can cause significant pain and discomfort. These plaques usually occur on the elbows, knees, legs, scalp, lower back, trunk and buttocks. Psoriasis may also affect the fingernails, toenails, soft tissues of the genitals, and inside the mouth. About 80% of patients have mild to moderate disease and 20% have moderate to severe psoriasis affecting more than 5% of body surface area (BSA) or areas such as the palms of the hands, soles the feet, face or genitals.[1] About 1 million of the people with psoriasis also have psoriatic arthritis (PsA). Triggers that may cause flare-ups of psoriasis include infections, stress, medications (e.g., lithium, beta adrenergic blockers), and changes that dry the skin. Other forms of psoriasis besides plaque type include guttate, pustular, inverse, and erythrodermic. Psoriasis may be associated with considerable physical and/or psychological disabilities. Treatment of psoriasis depends on the severity of the disease; the extent of disease (BSA involved); type of psoriasis; location of the lesions; symptoms; the patient's response to previous therapy; accessibility to a

dermatologist, hospital, and ultraviolet (UV) light facilities; and co-morbid disease states. Since psoriasis is a chronic disease, long-term safety of medications must be considered.

For plaque psoriasis, if the disease is limited, topical therapies with corticosteroids, vitamin D analogs (e.g., calcipotriene calcitriol), Taclonex® (betamethasone diproprionate/calcipotriene), Tazorac® (tazarotene), anthralin, coal tar preparations, keratolytics (salicylic acid, lactic acid, urea), topical moisturizers and combinations or sequential use of these topical therapies are indicated.[2,5] However, for patients with chronic plaque psoriasis that does not respond to topical therapies or patients with more extensive disease, systemic therapy may be used. The traditional systemic agents for plaque psoriasis are methotrexate (MTX), Soriatane® (acitretin tablets), and cyclosporine.[5] These medications may have significant adverse effects (e.g., hepatotoxicity, nephrotoxicity, teratogenicity). Other systemic agents have been investigated in psoriasis (e.g., azathioprine, tacrolimus, and mycophenolate mofetil). Phototherapy (e.g., ultraviolet B [UVB]) and photochemotherapy (psoralen and ultraviolet A **[**UVA] light [PUVA]) may also be used.[6-7] Soriatane is a first-line systemic agent for patients with chronic palmoplantar or pustular psoriasis, but it has a limited role in patients with plaque psoriasis.[7] Cyclosporine is a fast-acting agent commonly used for certain types of pustular or erythrodermic psoriasis. Cyclosporine is also used intermittently (up to 12 weeks) to control psoriasis flares. MTX may be used for plaque psoriasis; compared to cyclosporine, MTX has a moderate effect but can be used long-term. The biologics have established efficacy in plaque psoriasis. Narrow band (NB) UVB can be used in the physician's office or at home and is slightly less effective than PUVA.[1,6] The injectable biologic agents, Enbrel® (etanercept for subcutaneous [SC] injection), Humira® (adalimumab for SC injection), Remicade® (infliximab for intravenous [IV] infusion), and Stelara® (ustekinumab for SC injection) are options for patients who are candidates for phototherapy or systemic therapy, especially those who are intolerant of or unresponsive to traditional systemic agents.[7] Another agent available is Otezla, an oral phosphodiesterase 4 (PDE4) inhibitor that is indicated for treatment patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.[12]

Long-term safety is an important consideration.[7] The long-term risks of PUVA, MTX, and cyclosporine increase with cumulative dose. Safety concerns with the biologics include serious infections such as sepsis and tuberculosis, autoimmune conditions such as lupus and demyelinating disorders, and lymphoma. Patients with PsA, regardless of skin involvement, may require systemic therapy with MTX or a TNF antagonist such as Enbrel, Humira, or Remicade that are effective for both plaque psoriasis and PsA.[2] Of note, Simponi® (golimumab for SC injection) is a TNF blocker indicated for PsA, but not for plaque psoriasis.[8] Note that Otezla is also indicated in PsA, and it 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.[12] Warnings/Precautions for Otezla include depression, weight decrease, and drug interactions with strong cytochrome P450 inducers, and the most commonly observed adverse events (AEs) [incidence ≥ 5%] were diarrhea, nausea, and headache.

Almost all well-controlled clinical trials of psoriasis treatment include patients with chronic stable plaque psoriasis and exclude less common types of psoriasis and those involving the palms and soles, scalp, and intertriginous areas.[1]

One of the methods used to evaluate psoriasis in clinical trials is the psoriasis area-and-severity index (PASI) score.[1,9-10] The PASI ranges from 0 (no psoriasis) to 72 (the most severe disease possible) and combines the scores for the degree of erythema, induration, desquamation, and the percentage of BSA impacted. A primary endpoint in clinical trials is the PASI-75 which is ≥ 75% reduction from the baseline PASI score. Patients usually attain meaningful disease and quality of life improvements with at least a 50% decrease in PASI score.[10] Psoriasis severity (plaque, scaling, erythema) is also evaluated via global

assessments by the physician.[11] The static Physician Global Assessment (sPGA) is reported on a six- or seven-point scale (e.g., ranging from 5 = severe to 0 = none indicating the physician's overall assessment of psoriasis severity). Other dynamic PGA scales define the endpoint using scales such as "clear" or "minimal" or "almost clear". The Dermatology Life Quality Index (DLQI) has been used as a guide in patient management (e.g., for assessment of disease severity).[8]

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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 1) to reduce the risk of myocardial infarction (MI), stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease; and 2) as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe) for the treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH]) to reduce low-density lipoprotein cholesterol (LDL-C).[1] The safety and efficacy of Praluent in children have not been established.

Clinical Data

The efficacy of Praluent was assessed in several studies which mainly involved patients at high risk (e.g., background atherosclerotic cardiovascular disease, HeFH) who received Praluent along with maximally tolerated doses of statins, with or without other lipid-modifying therapies. The LDL-C reductions when Praluent was added onto statin therapy ranged from approximately 50% to 60% at the time of the efficacy endpoint evaluations (e.g., 12 or 24 weeks). Longer-term follow-up, including extension studies, are also available.[1]

ODYSSEY Outcomes was a Phase III, multicenter, international, randomized, double-blind, placebo-controlled cardiovascular (CV) outcomes trial involving Praluent (75 or 150 mg SC once every 2 weeks [Q2W]) used in addition to maximally tolerated statin therapy (n = 18,924) for up to 5 years among patients who had experienced a recent acute coronary syndrome (ACS) event.[1,2] The trial included patients who were ≥ 40 years of age who had experienced an ACS event (acute MI [83%] or unstable angina [17%]) within 1 to 12 months prior to randomization. Those involved in the trial had inadequate control of lipids (e.g., LDL-C ≥ 70 mg/mL, non high-density lipoprotein cholesterol [non-HDL-C] ≥ 100 mg/dL) despite receipt of high-intensity statins (atorvastatin 40 mg or 80 mg daily or rosuvastatin 20 or 40 mg daily) or maximally tolerated statins, with or without other lipid-modifying therapy. The primary endpoint was the time to the first occurrence of one of the following: coronary heart disease (CHD) death, non-fatal MI, fatal or non-fatal ischemic stroke, or unstable angina that required hospitalization. Other secondary endpoints were also evaluated (CV death, all-cause death, major CHD event). The mean patients age at baseline was 59 years and the mean LDL-C was 93 mg/dL.[1,2] Most patients (89%) were receiving high-dose atorvastatin (40 to 80 mg once daily [QD]) or rosuvastatin (20 to 40 mg QD); 8.5% of patients were on low to moderate dose atorvastatin/rosuvastatin and 3% of patients were on ezetimibe (with or without statin therapy).[2] The follow-up was a median of 2.8 years. At 4 months post-randomization, the mean LDL-C levels were 37.6 mg/dL and 93.3 mg/dL (on-treatment analysis), respectively, representing an approximate 62.7% decrease in LDL-C levels with adding Praluent. The primary endpoint occurred in 9.5% of patients (n = 903/9.462) given Praluent compared with 11.1% of patients (n = 1,052/9,462) given placebo (P < 0.001).[1,2] The number needed to treat to prevent one event was 63 patients. The event rates for the percentages of patients that comprised the primary endpoint (Praluent vs. placebo) included CHD death (2.2% vs. 2.3%; P = 0.38), non-fatal MI (6.6% vs. 7.6%), ischemic stroke (1.2% vs. 1.6%), and unstable angina (0.4% vs. 0.6%). All-cause death was also lower among patients assigned to Praluent (3.5%; n = 334/9,462) compared with placebo (4.1%; n = 392/9,462).

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 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).[3,4] Although LDL-C thresholds are not always recognized, in general, an LDL-C < 70 mg/dL is recommended in 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 (CAC) 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 FH.[14] FH 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 FH. High or moderate intensity statins are recommended; low potency statins are generally inadequate for patients with FH 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 FH 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 FH. 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 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.[18-20]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Praluent. 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. All approvals are provided for 3 years in duration.

Documentation: None required.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

149. Atherosclerotic Cardiovascular Disease (ASCVD) [Clinical].* Approve Praluent for 3 years if the patient meets the following criteria (A, B, C, and D):

G) The patient is ≥ 18 years of age; AND

H) 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 (MI) or has a history of an acute coronary syndrome (ACS); 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 (TIA); OR
- **iv.** The patient has peripheral arterial disease (PAD); OR
- **v.** The 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) 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 weeks; AND
  - **b)** The low-density lipoprotein cholesterol (LDL-C) level after this treatment 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; 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)** The patient meets all of the following [(1), (2), and (3)]:
    - **(1)** The 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) Praluent 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.

150. Heterozygous Familial Hypercholesterolemia [HeFH].* Approve Praluent for 3 years if the patient meets the following criteria (A, B, C, and D):

4. The patient is ≥ 18 years of age; AND

5. The patient meets one of the following criteria (i, ii, iii, iv, or v):

- **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 (LDLR), apolipoprotein B (APOB), proprotein convertase subtilisin kexin type 9 (PCSK9) or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) 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 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 [evolocumab injection for SC use]); OR

v. The 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.

6. 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 (LDL-C) level after this treatment 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; 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) The patient meets all of the following [(1), (2), and (3)]:

(1) The 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

7. Praluent 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.

151. Primary Hyperlipidemia.* Approve Praluent 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.

A) The patient is ≥ 18 years of age; AND

B) The patient has a coronary artery calcium or calcification (CAC) score ≥ 300 Agatston units; AND

C) The patient meets one of the following criteria (i or ii):

- **i.** The patient meets all of the following criteria (a, b and c):
  - **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
  - **b)** The 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)** The low-density lipoprotein cholesterol (LDL-C) level after this treatment regimen remains ≥ 100 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; 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)** The patient meets all of the following [(1), (2), and (3)]:
    - **(1)** The 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) Praluent 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

Praluent 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.)

101. 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.[21] 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).[22] The efficacy and safety of Repatha or Juxtapid in combination with Praluent have not been established.

102. 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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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
   (iii) 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: 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: 1) to reduce the risk of myocardial infarction (MI), stroke, and coronary revascularization in adults with established cardiovascular (CV) disease; 2) as an adjunct to diet, alone and in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for the treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH]) to reduce low-density lipoprotein cholesterol (LDL-C); and 3) 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.[1] 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.

Clinical Efficacy

The efficacy of Repatha was assessed in several studies which mainly involved patients at high risk (e.g., background atherosclerotic cardiovascular disease, HeFH) who received Repatha along with maximally tolerated doses of statins, with or without other lipid-modifying therapies. The LDL-C reductions when Praluent was added onto statin therapy ranged from approximately 50% to 60% at the time of the efficacy endpoint evaluations (e.g., 12 or 24 weeks).[1] Longer-term follow-up, including extension studies, are also available.

Cardiovascular (CV) Outcomes Data

The FOURIER (Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk) trial with Repatha was a randomized, double-blind, placebo-controlled event-driven trial involving over 27,000 patients with ASCVD with LDL-C levels ≥ 70 mg/dL.[1,2] Patients were between 40 and 85 years of age and had clinically evident ASCVD, defined as a history of MI, nonhemorrhagic stroke, or symptomatic peripheral arterial disease (PAD), as well as additional attributes that classified the patients at higher CV risk.[1,2] Patients were randomized to receive Repatha SC (either 140 mg Q2W or 420 mg QM) or placebo, in addition to background statin therapy (± ezetimibe). The primary efficacy endpoint was the composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. The average patient age was 62 years.[1,2] After 48 weeks of therapy, Repatha, in addition to background statin therapy, reduced LDL-C levels by 59% from a median baseline value of 92 mg/dL to 30 mg/dL.[2] The median duration of follow-up was 26 months. The primary endpoint occurred in 9.8% of patients (n = 1,344) randomized to Repatha plus background statin therapy compared with 11.3% of patients in the placebo group (n = 1,563) which received background statin therapy only, representing a statistically significant 15% reduction. The findings of this study suggest that lowering LDL-C levels with Repatha, in addition to continuing to receive background statin therapy, reduces the risk of adverse CV events among patients with background ASCVD. Death from any cause did not differ between the two groups (3.2% vs. 3.1%; P = 0.54).

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 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, TIA, or PAD.[10] Although LDL-C thresholds are not always recognized, in general, an LDL-C < 70 mg/dL is recommended in 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 CAC score ≥ 300 Agatston units are at an increased risk of CV events.[10-13]

In 2011, the NLA published guidelines for the screening, diagnosis, and management of pediatric and adult patients with FH.[14] FH 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 FH. High or moderate intensity statins are recommended; low potency statins are generally inadequate for patients with FH 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 FH 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.[23-24] Also, patients with an untreated LDL-C ≥ 190 mg/dL suggest FH.[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 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.[19,20]

HoFH is a rare inherited condition in which LDL-C is not adequately removed from the body, resulting in high levels of circulating LDL-C.[14,17] The 2014 HoFH position paper from the Consensus Panel on FH 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 LDLR, APOB, PCSK9, or LDLRAP1 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. 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. All approvals are provided for 3 years in duration.

Documentation: None required.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

152. Atherosclerotic Cardiovascular Disease (ASCVD) [Clinical].* Approve Repatha for 3 years if the patient meets the following criteria (A, B, C, and D):

- **K)** The patient is ≥ 18 years of age; AND
- **L)** 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 (MI) or has a history of an acute coronary syndrome (ACS); 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 (TIA); OR
iv. The patient has peripheral arterial disease (PAD); OR
v. The 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) 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 tablets ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND
b) The LDL-C level after this treatment 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; 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) The patient meets all of the following [(1), (2), and (3)]:
(1) The 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

N) Repatha 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.

153. Heterozygous Familial Hypercholesterolemia (HeFH).* Approve Repatha for 3 years if the patient meets the following criteria (A, B, C, and D):
8. The patient is ≥ 18 years of age; AND
9. The patient meets one of the following criteria (i, ii, iii, iv or v):
i. The patient has an untreated low-density lipoprotein cholesterol (LDL-C) ≥ 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 (LDLR), apolipoprotein B (APOB), proprotein convertase subtilisin kexin type 9 (PCSK9) or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) 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 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. The 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.

10. 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 tablets ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND

~~b)~~ The low-density lipoprotein cholesterol (LDL-C) level after this treatment 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; 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) The patient meets all of the following [(1), (2), and (3)]:

(1) The 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

11. Repatha 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.

154. Homozygous Familial Hypercholesterolemia (HoFH).* Approve Repatha for 3 years if the patient meets the following criteria (A, B, C, and D):

A) The patient is ≥ 13 years of age; AND

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

i. The 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. The patient has an untreated low-density lipoprotein (LDL-C) level > 500 mg/dL (prior to treatment with antihyperlipidemic agents); OR

iii. The 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. The 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) 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 (LDL-C) level after this treatment 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; 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) The patient meets all of the following criteria [(1), (2), and (3)]:

(1) The 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) Repatha 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.

155. Primary Hyperlipidemia.* Approve Repatha 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) The patient is ≥ 18 years of age; AND

F) The patient has a coronary artery calcium or calcification (CAC) score ≥ 300 Agatston units; AND

G) The patient meets one of the following criteria (i or ii):

i. The patient meets all of the following criteria (a, b, and c):

~~**a)**~~ The 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)~~ The 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)~~ The low-density lipoprotein cholesterol (LDL-C) level after this treatment regimen remains ≥ 100 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; 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) The patient meets all of the following [(1), (2), and (3)]:

(1) The 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) Repatha 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

Repatha 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.)

103. Concurrent use of Repatha with Praluent® (alirocumab injection for SC use) or Juxtapid (lomitapide capsules). Praluent is another PCSK9 inhibitor and should not be used with Repatha.[21] 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.[22] The efficacy and safety of using Praluent or Juxtapid in combination with Repatha have not been established.

104. 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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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
   (iv) 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: Psychiatry – Spravato Prior Authorization Policy
- Spravato™ (esketamine nasal spray – Janssen)

REVIEW DATE: 03/25/2020; selected revision 08/05/2020

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]

- **Treatment-resistant depression** (TRD) in adults.
- Depressive symptoms in adults with major depressive disorder (MDD) with **acute suicidal ideation or behavior**.

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.

Esketamine, the S-enantiomer of racemic ketamine, is a non-selective, non-competitive antagonist of the NMDA receptor, an ionotropic glutamate receptor.[1] The mechanism by which Spravato exerts its antidepressant effect is unknown.

Spravato should be administered in conjunction with an oral antidepressant.[1] 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. If a patient misses treatment sessions and there is worsening of depression symptoms, per clinical judgement, consider returning to the patient's previous dosing schedule (i.e., every two weeks to once weekly, weekly to twice weekly). For 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. Spravato must be administered under the direct supervision of a healthcare provider. A treatment session consists of nasal administration of Spravato and post-administration observation under supervision. The nasal spray device delivers a total of 28 mg of esketamine (two sprays of 14 mg each). Do not prime the device before use. Use two devices (56 mg) or three devices (84 mg), with a 5-minute rest between administrations of each device to allow the medication to absorb. During and after Spravato administration at each treatment session, observe the patient for at least 2 hours until the patient is safe to leave.

Disease Overview

Major depressive disorder is a serious, life-threatening condition with high rates of morbidity and a chronic disease course.[2] Over 17 million people in the US and over 300 million people worldwide have depression.[3,4] Major depressive disorder is considered the leading cause of disability worldwide and is also associated with increased mortality rates. 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 at least four weeks, leading to greater suffering, expense, and risk. For regulatory purposes, the FDA considers patients to have treatment-resistant depression if they have major depressive disorder 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. 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] Warnings/Precautions for Spravato also include dissociation. 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

247. 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) Spravato is being prescribed by a psychiatrist.

248. 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; 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) Spravato is being prescribed by a psychiatrist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Spravato 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.

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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

249. 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.)

222. Previous Treatment with Zulresso During the Current Episode of Postpartum Depression.

223. 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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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™ 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)

REVIEW DATE: 07/01/2020

OVERVIEW

Fluticasone propionate and salmeterol inhalation powder (Advair Diskus, generics), Advair HFA, AirDuo RespiClick (and authorized generic), Breo Ellipta, Dulera, and Symbicort 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] An additional ICS/LABA inhaler, AirDuo® Digihaler™ (fluticasone propionate and salmeterol inhalation powder), is available. It is a digital dry powder inhaler (DPI) with built-in sensors that connect to a companion mobile application and provide inhaler use information. AirDuo Digihaler has been approved by the FDA, but has not yet become available and therefore, it is not currently included in this policy. Of note, Wixela Inhub (fluticasone propionate/salmeterol inhalation powder) is a generic to Advair Diskus that was given a brand name by its manufacturer. Therefore, it is also included in this policy.

Fluticasone propionate and salmeterol inhalation powder (Advair Diskus, generics), Advair HFA, AirDuo RespiClick, fluticasone and salmeterol inhalation powder (authorized generic of AirDuo RespiClick), Breo Ellipta, Dulera, and Symbicort are indicated for the treatment of asthma. Fluticasone propionate and salmeterol inhalation powder (Advair

Diskus, generics) Breo Ellipta, and Symbicort are also indicated for the maintenance treatment of airflow obstruction and reducing exacerbations in patients with 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] AirDuo RespiClick (and authorized generic) also has not been studied in patients with COPD. However, this agent was filed as a New Drug Application (NDA) 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 AirDuo RespiClick, the literature and safety and effectiveness evidence supporting the approval and use of Advair Diskus are considered part of the evidence supporting the approval and use of AirDuo RespiClick. The indications for the ICS/LABA inhalers are in Table 1.

Table 1. FDA-Approved Indications.[1-6]

Brand (generic)	COPD*	Reduction of COPD Exacerbations†	Asthma (patients ≥ 18 years of age)	Asthma (patients 12 to 17 years of age)	Asthma (patients 4 to 12 years of age)
Fluticasone propionate and salmeterol inhalation powder (Advair Diskus®, generics)	X (250 mcg/50 mcg)	X (250 mcg/50 mcg)	X	X	X
Advair® HFA (fluticasone propionate and salmeterol inhalation aerosol)	--	--	X	X	--
AirDuo™ RespiClick® (fluticasone propionate and salmeterol inhalation powder; authorized generic)	--	--	X	X	--
Breo® Ellipta® (fluticasone furoate and vilanterol inhalation powder)	X (100 mcg/25 mcg)	X (100 mcg/25 mcg)	X	--	--
Dulera® (mometasone furoate and formoterol fumarate inhalation aerosol)	--	--	X	X	X (≥ 5 years)
Symbicort® (budesonide and formoterol fumarate inhalation aerosol)	X (160 mcg/4.5 mcg)	X (160 mcg/4.5 mcg)	X	X	X (≥ 6 years)

COPD – Chronic obstructive pulmonary disease; * Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and/or emphysema; † In patients with a history of chronic obstructive pulmonary disease exacerbations; -- Not indicated for the condition.

Guidelines

The 2020 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 are also recommended as initial as-needed 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.

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 RespiClick, fluticasone and salmeterol inhalation powder (authorized generic of AirDuo RespiClick), Breo Ellipta, Dulera, and 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 RespiClick, fluticasone and salmeterol inhalation powder (authorized generic of AirDuo RespiClick), Breo Ellipta, Dulera, or 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

Fluticasone propionate and salmeterol inhalation powder (Advair Diskus, generics [including Wixela Inhub]), Advair HFA, AirDuo RespiClick, fluticasone and salmeterol inhalation powder (authorized generic of AirDuo RespiClick), Breo Ellipta, Dulera, and Symbicort 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.)

105. **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. 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.

106. 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]

107. 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.

108. 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.

109. 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]

110. 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]

111. 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 (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]

112. 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]

113. 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]

114. 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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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® (roflumilast tablets – Astra Zeneca)

APPROVAL DATE: 10/23/2019

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.

Disease Overview

COPD is a common preventable and manageable lung disease.[2] Approximately 16 million people in the US are known to have COPD and it is estimated that many more have impaired lung function and undiagnosed disease.[20] COPD results in significant morbidity and mortality; in 2017, it was the fourth leading cause of death nationwide.[3] Exposure to tobacco smoke is considered to be the primary cause, but occupational exposures to chemical agents and fumes, indoor and outdoor air pollution, genetics, age, and socioeconomic status may also have a role in the development of COPD.[2] The disease itself is generally characterized by persistent respiratory symptoms and airflow limitation that is related to airway and/or alveolar abnormalities resulting from significant exposure to noxious particles or gasses. This airflow limitation is caused by both small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema). The most common symptoms of COPD are dyspnea, chronic cough, and/or sputum production. The goals of COPD treatment are to reduce symptoms, decrease the frequency and severity of exacerbations, and improve health status and exercise tolerance. None of the currently available medications for COPD have been found to modify the long-term decline in lung function that is hallmark to COPD disease progression.

Guidelines

The 2019 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.[2] Following initiation, therapies should adjusted as needed based on symptom severity and exacerbation risk. Daliresp is recommended in patients who continue to experience exacerbations despite long-acting muscarinic antagonist (LAMA)/long-acting beta$_2$-agonist (LABA) combination therapy and have a blood eosinophil level < 100 cells/microliter. Low blood eosinophils are

predictive of an insufficient response to inhaled corticosteroid (ICS) therapy, thereby making Daliresp a good option. Daliresp is also listed a possible option in patients receiving triple therapy with an ICS/LAMA/LABA who have an 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).

Clinical Efficacy

Daliresp has been studied in patients currently receiving treatment with bronchodilators (e.g., LABAs) and ICSs with or without additional therapy with a LAMA.[5-10] Five placebo-controlled clinical trials evaluated the effect of Daliresp on COPD exacerbations.[1,5-10] Two of these studies (n = 1,176) 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 (n = 3,096). In both trials, Daliresp demonstrated a significant reduction in the rate of moderate or severe exacerbations compared to placebo (15% to 18% reduction).

POLICY STATEMENT
Prior authorization is recommended for prescription benefit coverage of Daliresp. All approvals are provided for 3 years in duration unless otherwise 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 RespiClick, 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. An example of an inhaled corticosteroid/long-acting beta$_2$-agonist/long-acting muscarinic antagonist combination inhaler is Trelegy Ellipta.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Daliresp 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.)

115. Asthma. The efficacy of roflumilast (formulation not specified) in patients with asthma[11-14], allergic asthma[15,16], and exercise-induced asthma[17] 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) [2019] 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.[18,19]

116. 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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PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Adempas® (riociguat tablets – Bayer)

APPROVAL DATE: 09/11/2019

OVERVIEW

Adempas, a soluble guanylate cyclase (sGC) stimulator, is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) [World Health Organization {WHO} Group 4] after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class.[1] Adempas is also indicated for the treatment of adults with pulmonary arterial hypertension (PAH) [WHO Group 1], to improve exercise capacity, WHO functional class and to delay clinical worsening. Efficacy in WHO Group 1 PAH was established in patients receiving Adempas as monotherapy or in combination with endothelin receptor antagonists (ERAs) or prostanoids. Studies establishing effectiveness included mainly patients with WHO functional class II or III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%).

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 2009, the American College of Cardiology Foundation (ACCF) Task Force on Expert Consensus Documents and the American Heart Association (AHA), developed in collaboration with the ACCP, American Thoracic Society (ATS) and the Pulmonary Hypertension Association, published an expert consensus document on pulmonary hypertension.[2] The hemodynamic definition of PAH is a mean pulmonary artery pressure (mPAP) greater than 25 mmHg; a pulmonary capillary wedge pressure (PCWP), left atrial pressure (LAP) or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mmHg; and a pulmonary vascular resistance (PVR) greater than 3 Wood units. Many different medication from varying therapies classes and different routes of administration are recognized. In 2019, and updated CHEST guideline and Expert Panel Report regarding therapy for pulmonary arterial hypertension in adults was released.[3] Evidence for use of the many medications available is also detailed.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Adempas. 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. All approvals are provided for 3 years in duration unless otherwise noted below.

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 Indications

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 3 years if the patient meets all of the following criteria (i, ii, and iii):
- **i.** The patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
- **ii.** The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
- **iii.** The 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; OR

B) Patients Currently Receiving Adempas. Approve for 3 years if the patient meets all of the following criteria (i, ii, and iii):
- **i.** The patient has a diagnosis of WHO Group 1 PAH; AND
- **ii.** The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
- **iii.** The patient meets the following criteria (a and b):
  - **a)** The patient has had a right heart catheterization; AND
  - **b)** The results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH.

40. Chronic Thromboembolic Pulmonary Hypertension (CTEPH). Approve for 3 years if prescribed by, or in consultation with, a pulmonologist or a cardiologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Adempas 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.

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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PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Endothelin Receptor Antagonists
- Tracleer® (bosentan tablets and oral suspension – Actelion)
- Letairis® (ambrisentan tablets – Gilead, generics)

- Opsumit® (macitentan tablets – Actelion)

APPROVAL DATE: 09/11/2019

OVERVIEW

Tracleer, Letairis and Opsumit are oral endothelin receptor antagonists (ERAs) that are used for the treatment of pulmonary arterial hypertension (PAH).[1-3] Tracleer is indicated for the treatment of PAH (World Health Organization [WHO] Group 1) 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] In adults, trials establishing effectiveness included mainly patients with WHO Functional Class II to IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue disease (21%), and PAH associated with congenital heart disease with left-to-right shunts. Letairis is indicated for the treatment of PAH (WHO Group 1) to improve exercise ability and delay clinical worsening; and 2) for use in combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability.[2] Studies establishing effectiveness included predominantly those with WHO Functional Class II to III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%).[2] Opsumit is indicated for the treatment of PAH (WHO Group 1) to reduce the risks of disease progression and hospitalization for PAH.[3] The effectiveness was established in a long-term study involving patients with PAH who mainly had WHO Functional Class II to III symptoms who were treated for an average of 2 years. Patients had idiopathic and heritable PAH (57%), PAH due to connective tissue disorders (31%), and PAH due to congenital heart disease with repaired shunts (8%).

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) ≥ 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.

Chronic thromboembolic pulmonary hypertension (CTEPH) is a persistent obstruction of pulmonary arteries and is often a complication of pulmonary embolism.[6,7] 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 2009, the American College of Cardiology Foundation (ACCF) Task Force on Expert Consensus Documents and the American Heart Association (AHA), developed in collaboration with the American College of Chest Physicians (ACCP), American Thoracic Society (ATS) and the Pulmonary Hypertension Association, published an expert consensus document on pulmonary hypertension.[4] The hemodynamic definition of PAH is a mean pulmonary artery pressure (mPAP) greater than 25 mmHg; a pulmonary capillary wedge pressure (PCWP), left atrial pressure (LAP) or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mmHg; and a pulmonary vascular resistance (PVR) greater than 3 Wood units. Many different medication from varying therapies classes and different routes of administration are recognized.[5] In 2019, and updated CHEST guideline and Expert Panel Report regarding therapy for pulmonary arterial hypertension in adults was released. Evidence for use of the many medications available is also detailed.

Other Uses with Supportive Evidence

The BENEFiT (Bosentan Effects in iNopErable Forms of chronic Thromboembolic pulmonary hypertension) study was a double-blind trial involving 156 patients with CTEPH who were randomized to placebo or Tracleer therapy (target dose of 125 mg BID) for 16 weeks. Benefits were noted in some hemodynamic parameters (e.g., decreased pulmonary vascular resistance).[8] Adempas, 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.[9] The agent is also indicated for PAH (WHO Group 1) to improve exercise capacity, improve WHO functional class, and to delay clinical worsening. Adempas has a Boxed Warning regarding embryo-fetal toxicity and is contraindicated in patients using nitrates or nitric oxide donors in any forms, as well as in patients using PDE inhibitors. The main adverse effects of Adempas are symptomatic hypotension.

Tracleer has been used in patients with systemic sclerosis who have digital ulcers.[10-17] In a randomized, 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.[10] 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.[10] Another trial showed a reduction in the occurrence of new digital ulcers in patients given Tracleer for 24 weeks.[14] Many other agents are utilized in digital ulcers.[12,16] In 2017 the European League Against Rheumatism (EULAR) updated recommendations for the treatment of systemic sclerosis.[16] Tracleer has efficacy from two high-quality randomized controlled trials to reduce the number of new digital ulcers in patients with systemic sclerosis. 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 (PDE5) inhibitors or iloprost therapy.[16] A consensus of systemic sclerosis experts published an article that discusses therapy for digital ulcers.[15] The algorithm for digital ulcer prevention lists the following as first-line, second-line, third-line, and fourth-line treatment respectively: CCBs, PDE5 inhibitors, ERAs, and prostanoids. For the prevention of severe digital ulcers, selective sympathetecomy may occasionally be recommended. For active treatment CCBs are used first line, followed by PDE5 inhibitors.[15] A review on Raynaud's phenomenon and its manifestations (e.g., digital ulcers) also mentions similar medications. Other data describing use of epoprostenol are available.[18,19]

Safety

All agents are in Pregnancy Category X and have a Boxed Warning regarding teratogenicity.[1-3] Tracleer has a Boxed Warning regarding hepatotoxicity.[1] All agents have a Boxed Warning regarding embryofetal toxicity.[1-3]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Tracleer, Letairis, and Opsumit. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tracleer, Letairis, and Opsumit, 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. All approvals are provided for 3 years in duration unless otherwise noted below.

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 Tracleer, Opsumit, and Letairis 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):

C) Initial Therapy. Approve for 3 years if the patient meets all of the following criteria (i, ii, and iii).
- **i.** The patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
- **ii.** The agent is prescribed by or in consultation with a cardiologist or a pulmonologist; AND
- **iii.** The 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; OR

D) Patients Currently Receiving the Requested Endothelin Receptor Antagonist (i.e., Tracleer, Letairis or Opsumit). Approve for 3 years if the patient meets the following criteria (i, ii, and iii):
- **iv.** The patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
- **v.** The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
- **vi.** The patient meets the following criteria (a and b):
  - **a)** The patient has had a right heart catheterization; AND
  - **b)** The results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH.

Other Uses with Supportive Evidence

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

42. Chronic Thromboembolic Pulmonary Hypertension (CTEPH). Approve Tracleer for 3 years if the patient meets the following criteria (A and B):
- **A)** The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
- **B)** The patient meets ONE of the following conditions (i, ii, or iii):
  - **i.** The patient has tried Adempas; OR
  - **ii.** The patient has a specific contraindication to use of Adempas according to the prescribing physician.
    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; OR
  - **iii.** The patient is currently receiving Tracleer.

43. Digital Ulcers/Systemic Sclerosis. Approve Tracleer for 3 years if the patient meets the following criteria (A or B):
- **A)** The 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.
  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); OR
- **B)** The patient has tried one vasodilator/prostanoid therapy
  Note: Examples of vasodilator/prostanoid therapies include epoprostenol injection and alprostadil injection.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Letairis, Tracleer and Opsumit have 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.

117. 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. Letairis® tablets [prescribing information]. Foster City, CA: Gilead Sciences; August 2019.
3. Opsumit® tablets [prescribing information]. South San Francisco, CA: Actelion Pharmaceuticals; April 2019.
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18. Wigley FM, Flavahan NA. Raynaud's phenomenon. *N Engl J Med*. 2016;375(6):556-565.
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PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Epoprostenol injection

- Flolan® (epoprostenol injection – GlaxoSmithKline, generic)
- Veletri® (epoprostenol injection – Actelion)

APPROVAL DATE: 09/11/2019

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] Studies establishing effectiveness included predominantly patients with New York Heart Association (NYHA) Functional Class III to IV symptoms and etiologies of idiopathic or heritable PAH (49%) or PAH associated with connective tissue diseases (51%). It is administered as a continuous intravenous infusion.[1-3]

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.

CTEPH is a persistent obstruction of pulmonary arteries and is often a complication of pulmonary embolism.[6,7] 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 2009, the American College of Cardiology Foundation (ACCF) Task Force on Expert Consensus Documents and the American Heart Association (AHA), developed in collaboration with the ACCP, American Thoracic Society (ATS) and the Pulmonary Hypertension Association, published an expert consensus document on pulmonary hypertension.[4] The hemodynamic definition of PAH is a mean pulmonary artery pressure (mPAP) greater than 25 mmHg; a pulmonary capillary wedge pressure (PCWP), left atrial pressure (LAP) or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mmHg; and a pulmonary vascular resistance (PVR) greater than 3 Wood units. Many different medications from varying therapies classes and different routes of administration are recognized.

In 2019, and 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. In the absence of contraindications, patients with PAH should undergo acute vasoreactivity testing utilizing a short-acting agent (e.g., calcium channel blockers [CCBs]). 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.

Other Uses with Supportive Evidence

Epoprostenol injection has been used with varying results in patients with CTEPH.[8-10] It is sometimes used as a bridge prior to surgery. Limited options are available for patients with CTEPH.

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. 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. 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.

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 therapy is recommended in those who meet the following criteria:
FDA-Approved Indications

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. The patient has World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

ii. The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND

iii. The 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. The patient meets ONE of the following criteria (a or b):

a) The patient is in Functional Class III or IV; OR

b) The patient is in Functional Class II and meets ONE of the following criteria [(1) or (2)]:

(1) The patient has tried or is currently receiving one oral agent for PAH
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) and Uptravi® (selexipag tablets); OR

(2) The patient has tried one inhaled or parenteral prostacyclin product for PAH
Note: Examples of inhaled and parenteral prostacyclin products for PAH include Remodulin® (treprostinil injection [generic]), Ventavis® (iloprost inhalation solution), and Tyvaso® (treprostinil inhalation solution); AND

v. Patients with idiopathic PAH must meet ONE of the following criteria (a, b, c, d, or e):

a) The patient has had an acute response to vasodilator testing that occurred during the right heart catheterization (defined as a decrease in mPAP of at least 10 mm Hg to an absolute mPAP of less than 40 mm Hg without a decrease in cardiac output) AND has tried one oral calcium channel blocker (CCB) therapy
Note: Examples of CCBs include amlodipine and nifedipine extended-release tablets; OR

b) The patient did not have an acute response to vasodilator testing; OR
c) The patient cannot undergo a vasodilator test; OR
d) The patient cannot take CCB therapy (e.g., right heart failure, decreased cardiac output); OR
e) The patient has tried one CCB
Note: Examples of CCBs include amlodipine and nifedipine extended-release tablets; OR

B) Patients 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) The patient has World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
b) The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
c) The patient meets the following criteria [(1) and (2)]:
(1) The patient has had a right heart catheterization; AND
(2) The results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; 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.
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

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

Epoprostenol injection (Flolan, Veletri, generics) 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. 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

1. Flolan® injection for intravenous use [prescribing information]: Research Triangle Park: NC; GlaxoSmithKline; December 2018.
2. Epoprostenol sodium for injection [prescribing information]. North Wales, PA: Teva; March 2019.
3. Veletri® injection [prescribing information]. South San Francisco, CA: Actelion; December 2018.
4. 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.
5. 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.
6. Kim NH, Delcroix M, Jais X, et al. Chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2019;53(1):1801915.
7. Hoeper MM, Madani MM, Nakanishi N, et al. Chronic thromboembolic pulmonary hypertension. *Lancet Respir Med*. 2014;2(7):573-582.
8. Condliffe R, Kiely DG, Gibbs SR, et al. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. *Am J Respir Crit Care Med.* 2008;177:1122-1127.
9. Bresser P, Fedullo PF, Auger WR, et al. Continuous epoprostenol for chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2004; 23:595-600.
10. Cabrol S, Souza R, Jais X, et al. Intravenous epoprostenol in inoperable chronic thromboembolic pulmonary hypertension. *J Heart Lung Transplant*. 2007;26(4):357-362.

PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Inhaled Prostacyclin Products
- Ventavis® (iloprost inhalation solution – Actelion)
- Tyvaso® (treprostinil inhalation solution – United Therapeutics)

APPROVAL DATE: 09/11/2019

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. Studies establishing effectiveness involved mainly patients with NYHA Functional Class III to IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue diseases (23%).[1] Tyvaso is indicated for the treatment of PAH (WHO Group 1) to improve exercise ability.[2] Studies establishing effectiveness mainly included those with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).[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

In 2009, the American College of Cardiology Foundation (ACCF) Task Force on Expert Consensus Documents and the American Heart Association (AHA), developed in collaboration with the ACCP, American Thoracic Society (ATS) and the Pulmonary Hypertension Association, published an expert consensus document on pulmonary hypertension.[3] The hemodynamic definition of PAH is a mean pulmonary artery pressure (mPAP) greater than 25 mmHg; a pulmonary capillary wedge pressure (PCWP), left atrial pressure (LAP) or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mmHg; and a pulmonary vascular resistance (PVR) greater than 3 Wood units. Many different medication from varying therapies classes and different routes of administration are recognized.

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. 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. All approvals are provided for 3 years in duration unless otherwise noted below.

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

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):

A) Initial Therapy. Approve for 3 years if the patient meets the following criteria (i, ii, iii, and iv):

i. The patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

ii. The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND

iii. The patient meets ONE of the following criteria (a or b):

a) The patient is in Functional Class III or IV; OR

b) The patient is in Functional Class II and meets ONE of the following criteria [(1) or (2)]:

(1) The patient has tried or is currently receiving one oral agent for PAH.
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]), Adempas® (riociguat tablets), Orenitram® (treprostinil extended-release tablets), and Uptravi® (selexipag tablets); OR

(2) The patient has tried one inhaled or parenteral prostacyclin product for PAH.
Note: Examples of inhaled and oral 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

iv. The 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; OR

B) Patients 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. The patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

ii. The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND

iii. The patient meets the following criteria (a and b):

a) The patient has had a right heart catheterization; AND

b) The results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Ventavis and Tyvaso 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.

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

471. Ventavis® inhalation solution [prescribing information]. South San Francisco, CA: Actelion Pharmaceuticals; October 2017.
472. Tyvaso® inhalation solution [prescribing information]. Research Triangle Park, NC: United Therapeutics Corp.; October 2017.
473. 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.
474. 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.
475. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Orenitram® (treprostinil extended-release tablets – United Therapeutics)

APPROVAL DATE: 09/11/2019

OVERVIEW

Orenitram, an oral prostacyclin vasodilator, 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] The studies that established the efficacy of Orenitram included mainly patients with WHO functional class II to III symptoms and etiologies of idiopathic or heritable PAH (66%) or PAH associated with connective tissue disease (26%).

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 2009, the American College of Cardiology Foundation (ACCF) Task Force on Expert Consensus Documents and the American Heart Association (AHA), developed in collaboration with the ACCP, American Thoracic Society (ATS) and the Pulmonary Hypertension Association, published an expert consensus document on pulmonary hypertension.[2] The hemodynamic definition of PAH is a mean pulmonary artery pressure (mPAP) greater than 25 mmHg; a pulmonary capillary wedge pressure (PCWP), left atrial pressure (LAP) or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mmHg; and a pulmonary vascular resistance (PVR) greater than 3 Wood units. Many different medication from varying therapies classes and different routes of administration are recognized. In 2019, and 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. Because of the specialized skills required for evaluation and diagnosis of patients treated with Orenitram as well as the monitoring required for AEs and long-term efficacy, initial approval requires Orenitram to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 3 years in duration unless otherwise noted below.

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 Indications

47. 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.** The patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
- **ii.** The agent is prescribed by or in consultation with a cardiologist or a pulmonologist; AND
- **iii.** The 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.** The patient meets one of the following conditions (i or ii):

a) The 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).
Note: Examples of PDE5 inhibitors include Revatio® (sildenafil tablets and suspension [generic]) and Adcirca® (tadalafil tablets [generic]) and examples of ERAs include Tracleer® (bosentan tablets), Letairis® (ambrisentan tablets [generic]), and Opsumit® (macitentan tablets); OR

b) The patient is receiving or has received in the past for PAH one prostacyclin therapy or a prostacyclin receptor agonist (i.e., Uptravi) for PAH.
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]); OR

F) Patient Currently Receiving Orenitram. Approve for 3 years if the patient meets all of the following criteria (i, ii, and iii):

vii. The patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

viii. The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND

ix. The patient meets the following criteria (a and b):

a) The patient has had a right heart catheterization; AND

b) The results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Orenitram 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.)

118. 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. Orenitram® extended-release tablets [prescribing information]. Research Triangle Park, NC: United Therapeutics Corporation; October 2019.
477. McLaughlin VV, Archer SL, Badesch DB, et all; 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.
478. 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.

PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Phosphodiesterase Type 5 (PDE5) Inhibitors

- Adcirca® (tadalafil tablets [generic] – Eli Lilly/United Therapeutics)
- Alyq™ (tadalafil tablets [generic] – Teva)
- Revatio® (sildenafil tablets [generic], suspension [generic] and injection – Pfizer)

DATE REVIEWED: 09/18/2019

OVERVIEW

Revatio and Adcirca are phosphodiesterase type 5 (PDE5) inhibitors indicated for the treatment of pulmonary arterial hypertension (PAH).[1,2] Alyq is a generic to Adcirca.[7] Revatio is indicated for PAH (World Health Organization [WHO] Group I) in adults to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when Revatio was added to background epoprostenol injection therapy (Flolan® [generic], Veletri®). Studies establishing its effectiveness were short-term (12 to 16 weeks) and included mainly patients with New York Heart Association (NYHA) Functional Class II to III symptoms and idiopathic etiology (71%) or associated with connective tissue disease (25%).[1] Adcirca and Alyq are indicated for the treatment of PAH (WHO Group I) to improve exercise ability.[2,7] Studies establishing effectiveness were mainly in patients with NYHA Functional Class II to III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%). Sildenafil and tadalafil are also indicated as differently named brand products for the treatment of erectile dysfunction; tadalafil is also indicated for use in patients with benign prostatic hyperplasia.[3,4]

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.[5,6] 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 2009, the American College of Cardiology Foundation (ACCF) Task Force on Expert Consensus Documents and the American Heart Association (AHA), developed in collaboration with the ACCP, American Thoracic Society (ATS) and the Pulmonary Hypertension Association, published an expert consensus document on pulmonary hypertension.[5] The hemodynamic definition of PAH is a mean pulmonary artery pressure (mPAP) greater than 25 mmHg; a pulmonary capillary wedge pressure (PCWP), left atrial pressure (LAP) or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mmHg; and a pulmonary vascular resistance (PVR) greater than 3 Wood units. Many different medication from varying therapies classes and different routes of administration are recognized. In 2019, and updated CHEST guideline and Expert Panel Report regarding therapy for pulmonary arterial hypertension in adults was released.[6] Evidence for use of the many medications available is also detailed.

Safety

Revatio has a Warning regarding mortality with increasing doses in pediatric patients. In a long-term trial involving pediatric patients with PAH, an increase in mortality with increasing Revatio dose was noted.

Deaths were first observed following about 1 year and causes of death were usual of those with PAH. Revatio, especially chronic use, is not recommended in children.[1]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Revatio, Adcirca and Alyq. Because of the specialized skills required for evaluation and diagnosis of patients treated with Revatio, Adcirca and Alyq, 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. All approvals are provided for 3 years in duration unless otherwise noted below.

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 Revatio tablets, Revatio suspension, sildenafil suspension, Adcirca tablets and Alyq tablets is recommended in those who meet the following criteria:

48. 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.** The patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
- **ii.** The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist.
- **iii.** The 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; OR

H) Patients Currently Receiving the Requested Phosphodiesterase Type 5 (PDE5) inhibitor (i.e., Revatio tablets, Revatio suspension, sildenafil suspension or Adcirca). Approve for 3 years if the patient meets the following criteria (i, ii, and iii):

- **x.** The patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
- **xi.** The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND

xii. The patient meets the following criteria (a and b):
- **a)** The patient has had a right heart catheterization; AND
- **b)** The results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH).

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.** The patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
     - **ii.** The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
     - **iii.** The patient is unable to take an oral PDE5 inhibitor indicated for WHO Group 1 PAH. Note: Examples of oral PDE5 inhibitors for PAH include Revatio® (sildenafil tablets or suspension or suspension [generics]) and Adcirca® (tadalafil tablets [generic]); AND
     - **iv.** The 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; OR
   - **B)** Patients Currently Receiving Revatio Injection. Approve Revatio injection for 3 years if the patient meets the following criteria (i, ii, iii, and iv):
     - **i.** The patient has a diagnosis of World Health Organization (WHO) Group 1 PAH; AND
     - **ii.** The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
     - **iii.** The patient is unable to take an oral PDE5 inhibitor indicated for WHO Group 1 PAH. Note: Examples of oral PDE5 inhibitors for PAH include Revatio® (sildenafil tablets or suspension [generics]) and Adcirca® (tadalafil tablets [generic]); AND
     - **iv.** The patient meets the following criteria (a and b):
       - **a)** The patient has had a right heart catheterization; AND
       - **b)** The results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Revatio tablets, Revatio suspension, sildenafil suspension, Revatio injection, Adcirca or Alyq 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.)

2. **Erectile Dysfunction.** Coverage is not recommended. Patients should use other PDE5 inhibitors indicated for erectile dysfunction.

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; January 2019.
7. Adcirca® tablets [prescribing information]. Indianapolis, IN: Eli Lilly (marketed by United Therapeutics Corporation); August 2017.
8. Viagra® tablets [prescribing information]. New York, NY: Pfizer Labs; December 2017.
9. Cialis® tablets [prescribing information]. Indianapolis, IN: Eli Lilly; February 2018.
10. 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.
11. 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.
12. Alyq™ tablets [prescribing information]. North Wales, PA: Teva Pharmaceuticals; January 2019.

PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Remodulin® (treprostinil injection for subcutaneous or intravenous use – United Therapeutics Corporation, generics)

APPROVAL DATE: 09/11/2019

OVERVIEW

Treprostinil injection, a prostacyclin vasodilator, is indicated for the treatment of pulmonary arterial hypertension (PAH) [World Health Organization {WHO} Group 1] to diminish symptoms associated with exercise.[1,2] Studies establishing the effectiveness involved those with New York Heart Association (NYHA) Functional Class II to IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%). Treprostinil injection is also indicated for patients who require transition from epoprostenol, to reduce the rate of clinical deterioration. The risks and benefits of each agent should be considered carefully before transition. Treprostinil injection may be administered via continuous subcutaneous (SC) infusion or continuous intravenous infusion. Continuous SC infusion is the preferred route of administration. Use as an intravenous infusion if SC infusion is not tolerated.

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.

CTEPH is a persistent obstruction of pulmonary arteries and is often a complication of pulmonary embolism.[5,6] 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 2009, the American College of Cardiology Foundation (ACCF) Task Force on Expert Consensus Documents and the American Heart Association (AHA), developed in collaboration with the ACCP, American Thoracic Society (ATS) and the Pulmonary Hypertension Association, published an expert consensus document on pulmonary hypertension.[3] The hemodynamic definition of PAH is a mean pulmonary artery pressure (mPAP) greater than 25 mmHg; a pulmonary capillary wedge pressure (PCWP), left atrial pressure (LAP) or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mmHg; and a pulmonary vascular resistance (PVR) greater than 3 Wood units. Many different medications from varying therapies classes and different routes of administration are recognized.

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. In the absence of contraindications, patients with PAH should undergo acute vasoreactivity testing utilizing a short-acting agent (e.g., calcium channel blockers [CCBs]). 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.

Other Uses with Supportive Evidence

Treprostinil injection has been used with varying results in patients with CTEPH.[7-10] 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.

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. 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. 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.

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 Indications

49. 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. The patient has World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

ii. The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND

iii. The 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. The patient meets ONE of the following criteria (a or b):

a) The patient is in Functional Class III or IV; OR

b) The patient is in Functional Class II and meets ONE of the following criteria [(1) or (2)]:

(1) The patient has tried or is currently receiving one oral agent for PAH
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]), Orenitram® (treprostinil extended-release tablets) and Uptravi® (selexipag tablets); OR

(2) The patient has tried one inhaled or parenteral prostacyclin product for PAH
Note: Examples of inhaled and parenteral prostacyclin products for PAH include Ventavis® (iloprost inhalation solution), Tyvaso® (treprostinil inhalation solution), and epoprostenol injection (Flolan, Veletri, generics); AND

v. Patients with idiopathic PAH must meet ONE of the following criteria (a, b, c, d, or e):

a) The patient has had an acute response to vasodilator testing that occurred during the right heart catheterization (defined as a decrease in mPAP of at least 10 mm Hg to an absolute mPAP of less than 40 mm Hg without a decrease in cardiac output) AND has tried one oral calcium channel blocker (CCB) therapy
Note: Examples of CCBs include amlodipine and nifedipine extended-release tablets; OR

b) The patient did not have an acute response to vasodilator testing; OR

c) The patient cannot undergo a vasodilator test; OR

d) The patient cannot take CCB therapy (e.g., right heart failure, decreased cardiac output); OR

e) The patient has tried one CCB
Note: Examples of CCBs include amlodipine and nifedipine extended-release tablets; OR

B) Patients 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) The patient has World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
e) The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
f) The patient meets the following criteria [(1) and (2)]:
(3) The patient has had a right heart catheterization; AND
(4) The results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; 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.
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

50. 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

Treprostinil injection 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.)

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.[11]

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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PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Uptravi® (selexipag tablets – Actelion)

DATE REVIEWED: 09/11/2019; selected revision 02/12/2020

OVERVIEW

Uptravi, a selective non-prostanoid IP prostacyclin 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] The efficacy of Uptravi was established in a long-term study in patients with PAH with mostly WHO functional class II to III symptoms.

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 2009, the American College of Cardiology Foundation (ACCF) Task Force on Expert Consensus Documents and the American Heart Association (AHA), developed in collaboration with the ACCP, American Thoracic Society (ATS) and the Pulmonary Hypertension Association, published an expert consensus document on pulmonary hypertension.[2] The hemodynamic definition of PAH is a mean pulmonary artery pressure (mPAP) greater than 25 mmHg; a pulmonary capillary wedge pressure (PCWP), left atrial pressure (LAP) or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mmHg; and a pulmonary vascular resistance (PVR) greater than 3 Wood units. Many different medication from varying therapies classes and different routes of administration are recognized. In 2019, and 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.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Uptravi. Because of the specialized skills required for evaluation and diagnosis of patients treated with Uptravi as well as the monitoring required for AEs and long-term efficacy, initial approval requires Uptravi to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 3 years in duration unless otherwise noted below.

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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

51. 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.** The patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
  - **ii.** The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
  - **iii.** The 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 for the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND
  - **iv.** The patient meets ONE the of following conditions (a or b):
    - **a)** The 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).

Note: Examples of PDE5 inhibitors include Revatio® (sildenafil tablets and suspension [generic]) and Adcirca® (tadalafil tablets [generic]) and examples of ERAs include Tracleer® (bosentan tablets), Letairis® (ambrisentan tablets [generic]), and Opsumit® (macitentan tablets); OR

b) The patient is currently receiving, or has a history of receiving, one prostacyclin therapy for PAH.
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]); OR

J) Patients Currently Receiving Uptravi. Approve for 3 years if the patient meets all of the following criteria (i, ii, and iii):
- **i.** The patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
- **ii.** The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
- **iii.** The patient meets the following criteria (a and b):
  - **a)** The patient has had a right heart catheterization; AND
  - **b)** The results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Uptravi 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.)

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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PRIOR AUTHORIZATION POLICY

POLICY: Qbrexza™ (glycopyrronium cloth 2.4% for topical use – Dermira)

APPROVAL DATE: 10/09/2019

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 a competitive inhibitor of acetylcholine receptors, which are located on peripheral tissues, including sweat glands. Qbrexza inhibits the action of acetylcholine on sweat glands in hyperhidrosis, thereby reducing sweating. 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. It is administered by a single-use pre-moistened cloth supplied in an individual pouch. One single cloth should be used to apply Qbrexza to both underarms. Hands should be washed immediately with soap and water after applying and discarding the Qbrexza cloth. If Qbrexza comes in contact with the eyes it may cause temporary pupil dilation and blurred vision; avoid transfer of Qbrexza to the periocular area. Qbrexza should not be applied to broken skin or used with occlusive dressings.

Disease Overview

Hyperhidrosis is a skin disorder in which sweat is produced in excess of what is required to maintain normal body temperature.[2] It is categorized as either primary or secondary. Primary hyperhidrosis is idiopathic and presents in a bilateral and symmetrical pattern on the axilla, palms, soles, and face.[3] An underlying medical condition or use of a prescription medication generally results in secondary hyperhidrosis. Currently, the estimated prevalence of hyperhidrosis in the US is 4.8% (approximately 15.3 million people); 65% of these patients have axillary hyperhidrosis (equating to 3.12% of the US population or 9.9 million people).[2-3] Hyperhidrosis can range in severity with approximately 70% of patients with hyperhidrosis reporting severe excessive sweating in at least one part of the body.[2] This may result in restrictions in work and social relationships, limitations in physical and leisure activities, and emotional and mental health impairments. Low self-esteem and interpersonal difficulties have been reported to have a negative impact on daily activities; patients may also have impaired performance and productivity at work.[3] The exact etiology of hyperhidrosis is not completely understood.[3-4] However, it has been observed that patients with hyperhidrosis have a higher expression of acetylcholine and alpha-7 neuronal nicotinic receptor subunit in the sympathetic ganglia compared with controls.[4] Therefore, it has been hypothesized that excess sweating is caused by overstimulation of eccrine glands by sympathetic postganglionic nerve fibers releasing acetylcholine. The goal of the management of axillary hyperhidrosis is to decrease sweat production and sweat glands in an effort to ameliorate symptoms and improve quality of life.[4-5] There are some treatment options available in addition to modifications such as wearing lightweight clothing, replacing electrolytes lost in sweat, and maintaining a cold environment. Topical antiperspirants are first-line therapy for axillary hyperhidrosis. Over-the-counter (OTC) [e.g., aluminum zirconium tetrachlorohydrex gly] and prescription options (e.g., aluminum chloride hexahydrate 20% solution [Drysol™, generics]; Hypercare™ [aluminum chloride hexahydrate 15% solution], Xerac™ AC [aluminum chloride hexahydrate 6.25% solution]) are available. These agents work by blocking the openings of the sweat ducts. They are easy to use, but treatment with the prescription products is often limited by skin irritation. Other treatments have included topical anticholinergics (used off-label prior to the approval of Qbrexza) and botulinum toxin type A.

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 (2014).[6] 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

156. Hyperhidrosis, Primary Axillary. Approve for 1 year if the patient is ≥ 9 years of age.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Qbrexza 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.)

120. Hyperhidrosis, other than Primary Axillary. Qbrexza is not intended for application to areas other than the axillae.[1]

121. 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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PRIOR AUTHORIZATION POLICY

POLICY: Regranex® (becaplermin gel, 0.01% –Smith & Nephew)

REVIEW DATE: 07/15/2015

LAY CRITERIA EFFECTIVE DATE: Previously in Effect

OVERVIEW

Regranex is indicated for the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous (SC) tissue or beyond and have an adequate blood supply when used as an adjunct to, and not a substitute for, good ulcer care practices, including initial sharp debridement, pressure relief and infection control.[1] Regranex is a recombinant human platelet-derived growth factor (PDGF) for topical administration and has similar biological activity as endogenous PDGF, which promotes the chemotactic recruitment and proliferation of cells involved in wound repair and enhances the formation of granulation tissue.[1] The efficacy of Regranex has not been established for the treatment of pressure ulcers and venous stasis ulcers and has not been evaluated for the treatment of diabetic neuropathic ulcers that do not extend through the dermis into SC tissue (Stage I or II International Association Enterostomal Therapy [IAET] staging classification), or ischemic diabetic ulcers. The effects of Regranex on exposed joints, tendons, ligaments, and bone have not been established in humans.

Efficacy

Diabetic Ulcers

Published studies and combined meta-analyses have documented the efficacy of Regranex (0.01% and becaplermin gel 0.003%) in diabetic neuropathic ulcers.[2-6] The largest fully published trial[3] was a multicenter, double-blind, placebo-controlled study where 382 adults with type 1 or 2 diabetes and lower-extremity chronic ulcers (classified as Stage III or IV, as defined in the IAET guide to chronic wound staging) of at least 8 weeks duration were randomized to receive becaplermin gel 0.003%, Regranex, or placebo (vehicle gel) in addition to good wound care, which included debridement. Therapy continued until complete wound closure occurred or for a maximum of 20 weeks. Treatment with Regranex led to an increased incidence of complete healing by 43% compared with placebo (P = 0.007). Complete wound healing occurred in 50% of patients given Regranex (n = 61/123) compared with 35% of patients given placebo (n = 44/127). The time to achieve complete healing was decreased by 32% for patients given Regranex compared with placebo gel (86 days vs. 127 days, respectively; estimated 35th percentile, P = 0.013). Efficacy results with the becaplermin gel 0.003% were similar to those noted in the placebo group. In a 3-month follow-up evaluation, the incidence of ulcer recurrence was approximately 30% in all groups showing that the durability of ulcer closure was similar among the groups.

A published study compared the healing rates of Regranex (control agent) with OASIS® Wound Matrix after 12 weeks of treatment.[7] OASIS Wound Matrix is comprised of porcine-derived acellular small intestine submucosa, which is compatible with human tissue and is approved as a medical device and is indicated for the management of wounds including: partial- and full-thickness wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (abrasions, lacerations, second-degree burns, skin tears), drainage wounds, and surgical wounds (donor sites/grafts, post-Mohs' surgery, post-laser surgery, podiatric, wound dehiscence).[8-9] At the end of Week 12, the healing rate was 49% (n = 18/37) for OASIS vs. 28% (n = 10/36) for Regranex (P = 0.055). The mean time to healing was also not statistically different between the two groups (67 days for OASIS and 73 days for Regranex; P = 0.245). OASIS did have statistically significantly higher healing rates for plantar ulcers (52% [n = 14/27] vs. 14%

[n = 3/21] for Regranex; P = 0.014) and in patients with type 2 diabetes (63% [n = 12/19] vs. 29% [n = 8/28] for Regranex; P = 0.034), while there was no statistical difference in patients with type 1 diabetes (33% [n = 6/18] vs. 25% [n = 2/8] for Regranex; P = 1.0). At the 6-month follow-up, the recurrence rate for OASIS was 25% (n = 2/8) and for Regranex was 33% (n = 2/6). There was no overall difference in the rate of complications/adverse events (AEs) for OASIS (n = 17) and Regranex (n = 10), however, there was a higher number of wound infections in the study ulcer (n = 9) for OASIS than for Regranex (n = 3).

Regranex is the first platelet-derived topical growth factor to demonstrate therapeutic efficacy, albeit modest, in healing neuropathic ulcers. No similar agent exists and because there is a paucity of well-designed, placebo-controlled studies in the area of wound healing, comparison between different modalities are difficult.[3] Most cases of diabetic neuropathic ulcers heal with conventional ulcer care and data have suggested that a linear correlation may exist between the degree of aggressive debridement and the level of healing.[10-11] However, for diabetic patients that have poorly healing neuropathic ulcers, despite adequate perfusion and a reasonable trial of wound care, this product may provide benefits.[11]

Pressure Ulcers

Studies have also shown Regranex to have potential efficacy in the treatment of full thickness chronic pressure ulcers (Stage III or IV as defined by the National Pressure Ulcer Advisory Panel [NPUAP]).[14-16] In one trial, adults with non-healing full thickness pressure ulcers were given a standard regimen of good wound care and were randomized to one of four treatment arms for 16 weeks, which included Regranex (n = 31) and placebo gel (n = 31).[16] The incidence of complete healing was significantly greater for those given Regranex (23%), no patients receiving placebo had complete healing (P = 0.005). At least 90% healing was noted in 58% of patients given Regranex compared to 29% assigned to placebo gel (P = 0.021).

Other Ulcer/Wound Types

Regranex has also been used in other chronic non-healing ulcers. In one retrospective chart review, 11 out of 17 venous stasis ulcerations healed with use of Regranex in an average of 67.6 days.[21] In another retrospective chart review of Regranex use in patients with chronic lower extremity ulcers (venous ulcer, lipodermatosclerosis ulcer, neurotrophic [diabetic and non-diabetic] ulcers, and multifactorial [mixed arterial and venous] ulcers), 14 of the 21 target ulcers healed completely with a mean time to complete healing of 111.1 days.[22]

Reports in the literature also note Regranex being used for surgical wounds or for surgical wound dehiscense.[21,23-24] In a small double-blind, preliminary trial, patients (n = 21) with wound separation after cesarean delivery or benign abdominal gynecological procedures were randomized to receive Regranex or placebo (SurgiLube®) starting the day after the wound opened.[23] Wounds that were treated with Regranex closed more rapidly (35 ± 15 days) compared to those given placebo (54 ± 26 days; P = 0.05). Additional studies are needed to determine the effectiveness of Regranex for wound granulation and closure. Case reports and/or case series note that Regranex has also been used successfully for the treatment of ulcerated hemangiomas (including ulcerated perineal hemangiomas in infants),[25-26] chronic orbital ulcers,[27] scleroderma skin ulcers,[28] ulcerative lichen planus,[29] necrobiosis lipoidicum diabeticorum,[30] chronic irradiated wounds/ulcers (including wounds/ulcers with no granulation tissue at baseline),[31-33] wound dehiscence (following total laryngectomy) with pharyngocutaneous fistula,[24] and ulceration due to a stingray injury.[34]

Guidelines

Lower-Extremity Neuropathic Disease

Guidelines from the Wound Ostomy and Continence Nurses (WOCN) Society published in 2004 for the management of wounds in patients with lower-extremity neuropathic disease recommend that use of

Regranex can be considered for foot ulcers after necrotic tissue has been debrided, infection is cleared, and adequate perfusion has been established.[12]

Diabetic Ulcers

The Infectious Diseases Society of America (IDSA) guidelines for the diagnosis and treatment of diabetic foot infections recommend that all diabetic patients with a foot wound should receive appropriate wound care, which usually consists of debridement, redistribution of pressure off the wound to the entire weight-bearing surface of the foot, selection of dressings that allow for moist wound healing, and control excess exudation.[35] No adjunctive therapy has been proved to improve resolution of infection, but for selected diabetic foot wounds that are slow to heal, clinicians might consider using bioengineered skin equivalents, growth factors, granulocyte colony stimulating factors, hyperbaric oxygen therapy, or negative pressure wound therapy. The guidelines note that although an initial study with the PDGFs demonstrated benefit, subsequent investigations have not shown these treatments to improve healing, or they have been conducted in a fashion where the data cannot be interpreted in the context of routine care.

The 2005 g=Guidelines for diabetic foot care, developed by the Diabetes Committee of the American Orthopaedic Foot and Ankle Society, note that ulcers without a deep crater and with no bone exposed can be treated with sharp debridement of infected or necrotic tissue and surrounding thick callus.[13] Dry or moist saline dressings can be used in combination with therapeutic shoes or footwear in small ulcers. In addition, for larger ulcers the guidelines note that healing may be expedited with one of the newer hydrocolloid-type dressings, or platelet-derived wound healing factors.

Pressure Ulcers

Guidelines from the WOCN Society updated in 2010 for the prevention and management of pressure ulcers recommend that Regranex can be considered an adjunctive therapy to enhance the healing (treatment) of pressure ulcers (no stage specified).[17] Other guidelines and references have also supported the consideration of adjuvant use of Regranex or platelet-derived growth factor for managing pressure ulcers which are not healing with conventional therapy.[18-20]

Safety

In 2008, after a follow-up from the Food and Drug Administration (FDA) about the ongoing safety review of Regranex,[36-37] the Regranex package labeling was revised to include a boxed warning noting that in a post-marketing retrospective cohort study, there was an increased rate of mortality secondary to malignancy observed in patients treated with three or more tubes of Regranex.[1] Also, additional detail was added to the warnings section in regards to a follow-up study performed to monitor for any evidence of adverse events (AEs) such as increased numbers of cancers and a retrospective study of a medical claims database.[1,36-37] This additional detail notes that malignancies distant from the site of application have occurred in Regranex users in both a clinical study and in post-marketing use. An increased rate of death from systemic malignancies was seen in patients who have received three or more tubes of Regranex gel.[1] In the follow-up study, 491 of the 651 patients from two randomized, controlled studies were followed up for a median of 20 months to identify malignancies diagnosed after the end of the controlled studies. The rate of cancer diagnosis in this follow-up period was 3% (n = 8/291) for Regranex users and 1% (n = 2/200) for vehicle/standard of care users, providing a relative risk of 2.7 (95% Confidence Interval [CI]: 0.6, 12.8). The types of cancers were varied and all were remote from the treatment site. In the retrospective medical claims database study, the incidence and mortality rates of cancer were assessed in 1,622 Regranex users and 2,809 matched comparators. Both groups had a similar incidence rate of all cancers (10.2 per 1,000 person-years for Regranex and 9.1 per 1,000 person-years for the comparators (adjusted rate ratio 1.2 [95% CI: 0.7, 1.9]). However, there was more of a difference between the groups in regards to mortality from all cancers. The incidence rate of mortality from all cancers was 1.6 per 1,000 person-years for Regranex

users and 0.9 per 1,000 person-years for comparators (adjusted rate ratio 1.8 [95% CI: 0.7, 4.9]), but the most prominent difference was the mortality incidence from all cancers among patients who received three or more tubes of Regranex gel which was 3.9 per 1,000 person-years vs. 0.9 per 1,000 person-years for comparators (adjusted rate ratio 5.2 [95% CI: 1.6, 17.6]). The retrospective medical claims database involved diabetic patients aged 19 years and older with no history of cancer and similar diagnoses, similar drug use, and similar use of health services who were applying Regranex to foot and leg ulcers or who did not receive treatment with Regranex.[36-37] Because inadequately treated ulcers can lead to complications such as infections, especially foot ulcer infections which are a leading cause of hospitalization among diabetics, the FDA recommends that Regranex be used only when the benefits are expected to outweigh the risks described in the labeling.[37]

The average amount of Regranex gel used per patient has not been fully evaluated, but most likely is highly variable and dependent upon the area of the ulcer or wound and the timeframe of healing. In an open-label study using Regranex in diabetics with lower extremity ulcers, the average amount of Regranex gel used was 27.2 g (slightly less than two-15 g tubes) for patients with baseline target ulcers < 2 cm^2.[4] However, only 57% of patients in this study had a baseline ulcer of this size. Another study comparing Regranex use with the OASIS Wound Matrix in diabetic ulcer patients also had similar Regranex usage of slightly less than two-15 g tubes per patient.[7] And a retrospective chart review study of 51 patients with lower extremity ulcerations due to various causes had an average Regranex tube use of 1.8 tubes per patient (tube size was not described).[21] In addition, 78% (n = 40/51) of these patients used two or fewer Regranex tubes.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Regranex. All approvals are provided for *5 months* unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

Food and Drug Administration (FDA)-Approved Indications

1. **Lower Extremity Diabetic Neuropathic Ulcer(s) that is/are Classified as Stage III or IV** (see addendum for NPUAP classification system).[1] Approve for 5 months if Regranex is used in adjunct to good ulcer/wound care practices (e.g., sharp debridement, pressure relief, and infection control).

   Regranex is indicated for the treatment of lower extremity diabetic neuropathic ulcer(s) that extend into the subcutaneous (SC) tissue or beyond and have good blood supply.[1] Regranex is indicated as an adjunct to, and not a substitute for, good ulcer/wound care practices including initial sharp debridement, pressure relief, and infection control.

Other Uses with Supportive Evidence

2. **Clean and Granulating Ulcer/Wound Classified as Stage II** (e.g., Stage II diabetic neuropathic ulcers and pressure ulcers). Approve if the patients meets the following criteria A and B.
   A) The patient has tried one other standard ulcer/wound care therapy (e.g., debridement, topical therapies [collagenase]) for at least 4 weeks; AND

B) Regranex will be used in adjunct to good ulcer/wound care practices (e.g., sharp debridement, pressure relief, and infection control).

In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

3. **Granulating Ulcer/Wound** (e.g., pressure ulcers, venous stasis ulcers, other diabetic ulcers) **Classified as Stage III or IV**[14-20,24-26,28,31-34] (see addendum NPUAP classification system[38-39]). Approve if Regranex is used in adjunct to good ulcer/wound care practices (e.g., sharp debridement, pressure relief, and infection control).

   Several studies[14-16] and case reports and/or case series[24-26,28,31-34] have found Regranex to be efficacious for treating/healing other non-diabetic neuropathic ulcers or wounds classified as Stage III or above. In addition, the WOCN Pressure Ulcer guidelines[17] list Regranex as an adjunctive therapy in the healing of pressure ulcers, and other references from the Wound Healing Society,[18] Canadian Association of Wound Care,[19] and a recent review[20] also support consideration of use of Regranex for treating non-healing chronic pressure ulcers. Regranex is indicated as an adjunct to, and not a substitute for, good ulcer/wound care practices including initial sharp debridement, pressure relief, and infection control.[1]

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Regranex 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.)

Coverage of Regranex is not recommended in the following circumstances:

122. **First-Line Therapy for the Treatment of Stage II Ulcers/Wounds.** Standard ulcer/wound care should be used first-line.

123. **Prevention of Ulcers/Wounds.** The efficacy of Regranex for prevention has not been evaluated.

124. **Treatment of Wounds/Ulcers Classified as Stage I.** These wounds are not open and therefore are not appropriate for Regranex therapy.

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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ADDENDUM

National Pressure Ulcer Advisory Panel (NPUAP) Pressure Ulcer Stages[38-39]
NPUAP Pressure Ulcer Stage Definitions[38-39]
Suspected Deep Tissue Injury: Purple or maroon localized area of discolored intact skin or blood-filled blister due to damage of underlying soft tissue from pressure and/or shear. The area may be preceded by tissue that is painful, firm, mushy, boggy, warmer or cooler as compared to adjacent tissue.

Stage I: Intact skin with non-blanchable redness of a localized area usually over a bony prominence. Darkly pigmented skin may not have visible blanching; its color may differ from the surrounding area.

Stage II: Partial-thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed, without slough. May also present as an intact or open-ruptured serum-filled blister.

Stage III: Full-thickness tissue loss. Subcutaneous fat may be visible but bone, tendon, or muscle are not exposed. Slough may be present but does not obscure the depth of tissue loss. May include undermining and tunneling.

Stage IV: Full-thickness tissue loss with exposed bone, tendon or muscle. Slough or eschar may be present on some parts of the wound bed. Often include undermining and tunneling.

Unstageable: Full thickness tissue loss in which the base of the ulcer is covered by slough (yellow, tan, gray, green or brown) and/or eschar (tan, brown or black) in the wound bed.

* Note that the WOCN was formerly called the International Association of Enterostomal Therapy (IAET).[11,16]

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Rituximab Intravenous Products

- Rituxan® (rituximab for intravenous infusion – Genentech)
- Ruxience™ (rituximab-pvvr IV injection – Pfizer)
- Truxima® (rituximab-abbs injection for intravenous use – Celltrion/Teva)

DATE REVIEWED: 06/03/2020 **[Effective 07/01/2020]**

OVERVIEW

Rituximab products are CD20-directed cytolytic antibodies. All approved rituximab intravenous products are indicated for treatment of the following conditions:

6. **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; AND
   - for relapsed or refractory, low-grade or follicular, CD20-positive, B-cell, disease; AND
   - 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; AND
   - for previously untreated diffuse large B-cell, CD20-positive disease, in combination with cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) or other anthracycline-based chemotherapy regimens; AND
7. **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; AND
8. **Granulomatosis with polyangitis** (GPA) [Wegener's granulomatosis {WG}] and **microscopic polyangiitis** (MPA) in adults, in combination with glucocorticoids.

In addition to the above indications, Rituxan IV and Truxima are also indicated for treatment of the following condition:

3. **Rheumatoid arthritis** (RA), in adult patients with moderately to severely active disease, in combination with methotrexate (MTX) for patients who have had an inadequate response to one or more tumor necrosis factor inhibitors (TNFis).

In addition to the above indications, Rituxan IV is also indicated for treatment of the following conditions:

1. **Pemphigus vulgaris**, for adults with moderate to severe; AND
2. **Granulomatosis with polyangitis** (GPA) [Wegener's granulomatosis {WG}] and **microscopic polyangiitis** (MPA) in patients ≥ 2 years of age, in combination with glucocorticoids.

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 non-Hodgkin's lymphomas (NHLs). B-cells are thought to play a role in the pathogenesis of rheumatoid arthritis (RA) and associated chronic synovitis.

Ruxience and Truxima are approved as biosimilar to Rituxan intravenous (IV), 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 products 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]

- **Vasculitis:** EULAR/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]
- National Comprehensive Cancer Network (NCCN) guidelines:[6]
  - **CLL/SLL:** 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]
  - **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]
  - **Acute Lymphoblastic Leukemia (ALL):** Guidelines (version 1.2020 – January 15, 2020) list rituximab in multiple induction regimens for Philadelphia chromosome (Ph)-negative disese.[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.
  - **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]
  - **Graft Versus Host Disease:** Guidelines (version 2.2020 – March 23, 2020) list rituximab among the agents used for steroid-refractory chronic GVHD.[15]
- **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 DMARD.[16]
- **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]
- **Systemic Lupus Erythematous (SLE):** 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]

Safety

Rituximab IV products have Boxed Warnings due to fatal infusion reactions, severe mucocutaneous reactions, hepatitis B virus (HBV) reactivation, and progressive multifocal leukoencephalopathy (PML). Deaths within 48 hours of rituximab infusions have been reported, primarily (80%) associated with the first infusion. Screen all patients for HBV infection and monitor during and after treatment with rituximab IV. Discontinue rituximab products in cases of HBV reactivation.

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 IV products is recommended in those who meet the following criteria:

FDA-Approved Indications

34. 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. The 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 requested agent is being administered in combination with glucocorticoids; AND
c. The agent 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 (Note: This includes patients who received induction treatment using a rituximab

product or other standard of care immunosuppressants). Approve for 1 year if the patient meets BOTH of the following (i and ii):

~~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.

35. Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL). Approve for 1 year if prescribed by or in consultation with an oncologist.

36. B-Cell Lymphoma (Note: Examples of B Cell Lymphomas include Follicular Lymphoma, Diffuse Large B-Cell Lymphoma [DLBCL], 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). Approve for 1 year if prescribed by or in consultation with an oncologist.

37. 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 agent 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 agent is prescribed by or in consultation with a dermatologist.

38. Rheumatoid Arthritis (RA). 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. The 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 for RA are not required to "step back" and try a conventional synthetic DMARD.

ii. The agent 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 SC], Actemra [IV or SC], Kevzara, Kineret, and Orencia [IV or SC]). Examples of targeted synthetic DMARDs include Xeljanz/XR, Olumiant, and Rinvoq.

iii. The requested agent 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 (RA). 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 (ALL). Approve for 1 year if the patient meets ALL of the following (A and B):

A) The patient has CD20-positive disease; AND

B) The agent is prescribed by or in consultation with an oncologist.

19. Graft Versus Host Disease (GVHD). Approve for 1 year if the patient meets BOTH of the following (A and B):

i. The 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 agent is prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center.

20. Hairy Cell Leukemia. Approve for 1 year if the patient meets BOTH of the following conditions (A and B):

A) The patient has relapsed/refractory hairy cell leukemia; AND

B) The agent is prescribed by or in consultation with an oncologist.

21. Hodgkin Lymphoma. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) The patient has nodular lymphocyte-predominant disease; AND

B) The agent 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. The 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. The 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) The patient has had an inadequate response or was unable to tolerate at least ONE other disease-modifying agent for MS; AND

B) The agent will not be used concurrently with another disease-modifying agent used for multiple sclerosis; AND
Note: Examples of disease-modifying agents for MS 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 requested agent 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 (NMO) 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. The 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 agent 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

Rituximab IV 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. (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.

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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 – Rituximab Intravenous Products

- Rituxan® (rituximab for intravenous infusion – Genentech)
- Ruxience™ (rituximab-pvvr IV injection – Pfizer)
- Truxima® (rituximab-abbs injection for intravenous use – Celltrion/Teva)

DATE REVIEWED: 06/03/2020

OVERVIEW
Rituximab products are CD20-directed cytolytic antibodies. All approved rituximab intravenous products are indicated for treatment of the following conditions:

9. **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; AND
   - for relapsed or refractory, low-grade or follicular, CD20-positive, B-cell, disease; AND
   - 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; AND
   - for previously untreated diffuse large B-cell, CD20-positive disease, in combination with cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) or other anthracycline-based chemotherapy regimens; AND
10. **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; AND
11. **Granulomatosis with polyangitis** (GPA) [Wegener's granulomatosis {WG}] and **microscopic polyangiitis** (MPA) in adults, in combination with glucocorticoids.

In addition to the above indications, Rituxan IV and Truxima are also indicated for treatment of the following condition:

4. **Rheumatoid arthritis** (RA), in adult patients with moderately to severely active disease, in combination with methotrexate (MTX) for patients who have had an inadequate response to one or more tumor necrosis factor inhibitors (TNFis).

In addition to the above indications, Rituxan IV is also indicated for treatment of the following conditions:

3. **Pemphigus vulgaris**, for adults with moderate to severe; AND
4. **Granulomatosis with polyangitis** (GPA) [Wegener's granulomatosis {WG}] and **microscopic polyangiitis** (MPA) in patients ≥ 2 years of age, in combination with glucocorticoids.

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 non-Hodgkin's lymphomas (NHLs). B-cells are thought to play a role in the pathogenesis of rheumatoid arthritis (RA) and associated chronic synovitis.

Ruxience and Truxima are approved as biosimilar to Rituxan intravenous (IV), 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 products 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]

- **Vasculitis:** EULAR/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]
- National Comprehensive Cancer Network (NCCN) guidelines:[6]
  - **CLL/SLL:** 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]
  - **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]
  - **Acute Lymphoblastic Leukemia (ALL):** Guidelines (version 1.2020 – January 15, 2020) list rituximab in multiple induction regimens for Philadelphia chromosome (Ph)-negative disese.[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.
  - **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]
  - **Graft Versus Host Disease:** Guidelines (version 2.2020 – March 23, 2020) list rituximab among the agents used for steroid-refractory chronic GVHD.[15]
- **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 DMARD.[16]
- **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]
- **Systemic Lupus Erythematous (SLE):** 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]

Safety

Rituximab IV products have Boxed Warnings due to fatal infusion reactions, severe mucocutaneous reactions, hepatitis B virus (HBV) reactivation, and progressive multifocal leukoencephalopathy (PML). Deaths within 48 hours of rituximab infusions have been reported, primarily (80%) associated with the first infusion. Screen all patients for HBV infection and monitor during and after treatment with rituximab IV. Discontinue rituximab products in cases of HBV reactivation.

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 IV products is recommended in those who meet the following criteria:

FDA-Approved Indications

39. Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis. Approve for the duration noted if the patient meets ONE of the following (A or B):

D) Induction Treatment. Approve for 1 month if the patient meets ALL of the following (i, ii, and iii):

a. The 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 requested agent is being administered in combination with glucocorticoids; AND
c. The agent is prescribed by or in consultation with a rheumatologist, nephrologist, or immunologist.

~~E)~~ Follow-Up Treatment of Patients Who Have Received Induction Treatment for ANCA-Associated Vasculitis (Note: This includes patients who received induction treatment using a rituximab product or other standard of care immunosuppressants). Approve for 1 year if the patient meets BOTH of the following (i and ii):

~~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.

40. Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL). Approve for 1 year if prescribed by or in consultation with an oncologist.

41. B-Cell Lymphoma (Note: Examples of B Cell Lymphomas include Follicular Lymphoma, Diffuse Large B-Cell Lymphoma [DLBCL], 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). Approve for 1 year if prescribed by or in consultation with an oncologist.

42. 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 agent 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 agent is prescribed by or in consultation with a dermatologist.

43. Rheumatoid Arthritis (RA). 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):

iv. The 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 for RA are not required to "step back" and try a conventional synthetic DMARD.

v. The agent 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 SC], Actemra [IV or SC], Kevzara, Kineret, and Orencia [IV or SC]). Examples of targeted synthetic DMARDs include Xeljanz/XR, Olumiant, and Rinvoq.

vi. The requested agent 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 (RA). 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):

ii. 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.

iii. 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 (ALL). Approve for 1 year if the patient meets ALL of the following (A and B):
A) The patient has CD20-positive disease; AND
B) The agent is prescribed by or in consultation with an oncologist.

22. Graft Versus Host Disease (GVHD). Approve for 1 year if the patient meets BOTH of the following (A and B):
i. The 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 agent is prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center.

23. Hairy Cell Leukemia. Approve for 1 year if the patient meets BOTH of the following conditions (A and B):
A) The patient has relapsed/refractory hairy cell leukemia; AND
B) The agent is prescribed by or in consultation with an oncologist.

24. Hodgkin Lymphoma. Approve for 1 year if the patient meets BOTH of the following (A and B):
C) The patient has nodular lymphocyte-predominant disease; AND
D) The agent 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):
C) Initial Therapy. Approve for 1 month if the patient meets BOTH of the following (i and ii):
i. The 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.
D) 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. The 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):

E) The patient has had an inadequate response or was unable to tolerate at least ONE other disease-modifying agent for MS; AND

F) The agent will not be used concurrently with another disease-modifying agent used for multiple sclerosis; AND

Note: Examples of disease-modifying agents for MS 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).

G) The requested agent is prescribed by or in consultation with a physician who specializes in the treatment of MS and/or a neurologist; AND

H) 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 (NMO) 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):

C) Initial Therapy. Approve for 1 month (adequate duration to receive one course) if the patient meets BOTH of the following (i and ii):

i. The 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 agent is prescribed by or in consultation with a rheumatologist, nephrologist, or neurologist.

D) 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).

15. Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma. Approve for 1 year if prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Rituximab IV 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. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

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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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® (afamelanotide implant for subcutaneous use – Clinuvel)

DATE REVIEWED: February 19, 2020

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] The agent 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]

Two subtypes of EPP exist which differ in their genetic inheritance patterns. Classic EPP is inherited in an autosomal recessive fashion (sometimes referred to as EPP-AR). In this form of EPP, mutations in the *FECH* gene lead to decreased activity of ferrochelatase, the final enzymatic step in heme biosynthesis.[4] This results in accumulation of an intermediate metabolite called protoporphyrin. An X-linked subtype of EPP, often referred to in the literature 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 the erythroid form of 5-aminolevulinate synthase 2 (ALAS2). This enzyme is responsible for an earlier step in heme biosynthesis; hyperactivity of the ALAS2 enzyme leads 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 accumulates in the bone marrow and is taken up by the liver and vascular endothelium.[3,4] 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] Some patients may also be sensitive to artificial light, as the photosensitivity is primarily due to visible blue light.[5,6] 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

250. Erythropoietic Protoporphyria (Including X-Linked Protoporphyria). 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 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

Scenesse 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.)

224. 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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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

12. 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.)

225. 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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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: Selzentry® (maraviroc tablets – Pfizer)

REVIEW DATE: 06/10/2016

LAY CRITERIA EFFECTIVE DATE: Previously in Effect

OVERVIEW

Selzentry, in combination with other antiretroviral therapy (ART), is indicated for the treatment of adults with only cysteine-cysteine chemokine receptor 5 (CCR5)-tropic human immunodeficiency virus (HIV)-1.[1] This indication is based on analyses of plasma HIV-1 RNA levels in two controlled trials of Selzentry in treatment-experienced patients and one trial in treatment-naïve patients. Both trials in treatment-experienced patients were conducted in clinically advanced, three-class ART-experienced adults with evidence of HIV-1 replication despite ongoing ART therapy. When initiating therapy with Selzentry, the following should be considered:

- Adult patients infected with only CCR5-tropic HIV-1 should use Selzentry.
- Tropism testing must be conducted with a highly sensitive tropism assay that has demonstrated ability to identify patients appropriate for use of Selzentry. Outgrowth of pre-existing low-level cysteine-X-cysteine chemokine receptor 4 (CXCR4)- or dual-mixed tropic HIV-1 not detected by tropism testing at screening has been associated with virologic failure of Selzentry.
- Use of Selzentry is not recommended in patients with dual/mixed- or CXCR4-tropic HIV-1 as efficacy was not demonstrated in a Phase II study.
- The safety and efficacy of Selzentry have not been established in pediatric patients.
- In treatment-naïve patients, more patients treated with Selzentry experienced virologic failure and developed lamivudine resistance compared with Sustiva® (efavirenz tablets/capsules)-treated patients.

Selzentry is the only Food and Drug Administration (FDA-approved) CCR5 antagonist and works by selectively binding to the human chemokine receptor CCR5 preventing the interaction necessary for CCR5-tropic HIV-1 to enter cells. CXCR4-tropic and dual/mixed-tropic (e.g., CCR5/CXCR4) HIV-1 entry is not inhibited by Selzentry; the antiviral activity of Selzentry against HIV-2 has not been evaluated.

Co-receptor tropism assay should be performed whenever the use of CCR5 antagonist is being considered.[2] Phenotypic co-receptor tropism assays have been used in clinical practice. A genotypic assay to predict co-

receptor use is now commercially available and is less expensive than phenotypic assays. Evaluation of genotypic assays is ongoing; however, data suggest that testing should be considered as an alternative assay. The same principles regarding testing for co-receptor use also apply to testing when patients exhibit virologic failure on a CCR5 antagonist. Resistance to CCR5 antagonists in the absence of detectable CXCR4- using virus has been reported, but such resistance is uncommon. The Department of Health and Human Services (DHHS) guidelines make the following recommendations regarding co-receptor tropism assays: 1) A co-receptor tropism assay should be performed whenever the use of CCR5 co-receptor antagonist is being considered; 2) co-receptor tropism testing is also recommended for patients who exhibit virologic failure on a CCR5 antagonist; 3) a phenotypic assay is preferred to determine HIV-1 co-receptor usage; and 4) a genotypic tropism assay should be considered as an alternative test to predict HIV-1 co-receptor usage.

Two Trofile® assays are now available.[3] One Trofile assay if for patients with HIV RNA ≥ 1,000 copies/mL (Trofile) and the other is for patients with HIV RNA < 1,000 copies/mL (Trofile DNA). The Trofile assay is 100% sensitive at detecting 0.3% CXR4-using minor variant and uses the complete gp160 coding region of the HIV-1 envelope protein to ensure that all determinants of tropism are tested. The Trofile DNA is for patients with ***undetectable*** viral loads, and can be considered when a patient's viral tropism is unknown, and a CCR5 antagonist is desired. Unlike the standard Trofile assay, which uses viral RNA found in the plasma of patients with viral loads ≥ 1,000 copies/mL, Trofile DNA uses viral DNA extracted from cells in a whole blood draw. Once the viral information is obtained, Trofile DNA runs on the same clinically validated platform as the Trofile.

Clinical Efficacy

The clinical efficacy and safety of Selzentry have been established from analyses of data from three ongoing studies in adults infected with CCR5-tropic HIV-1 (two studies in ART-experienced patients[1] and one in ART-naïve patients[7]). These studies are supported by a 48-week study in ART-experienced adults infected with dual/mixed-tropic HIV-1.[4] In both treatment-experienced and treatment-naïve patients, detection of CXCR4-using virus prior to initiation of therapy has been associated with a reduced virologic response to Selzentry.[1] In the majority of cases, treatment failure on Selzentry in treatment-experienced patients with HIV-1 was associated with the detection of CXCR4- or dual/mixed-tropic virus.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Selzentry. All approvals are provided for 3 years unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

4. **HIV-1 Infection with Cysteine-Cysteine Chemokine Receptor 5 (CCR5)-Tropic Virus.** Approve for patients who meet the following criteria (A and B):
   A) The patient has HIV-1 infection; AND
   B) The patient has only CCR5-tropic virus detected by an enhanced sensitivity tropism assay.

Selzentry is indicated for use in combination with other antiretroviral agents, for patients infected with only CCR5-tropic HIV-1.[1] Only patients with CCR5-tropic HIV-1 should use Selzentry tablets.[1]

The DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents recommend the use of coreceptor tropism assays in clinical practice whenever the use of a CCR5 inhibitor is being considered.[2] Although Selzentry may be active against some HIV-2 isolates, there are no approved assays to determine HIV-2 coreceptor tropism. Further, HIV-2 is known to utilize multiple minor coreceptors in addition to CCR5 and CXCR4.

Other Uses with Supportive Evidence

2. **Patients with HIV-1 Infection Already Started on Selzentry.** Approve.
In the professional opinion of a specialist physician, we have adopted this criterion.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Selzentry 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.)

126. **HIV-1 Infection with CXCR4- or CCR5/CXCR4-Tropic Virus**. Selzentry is not indicated in patients with CXCR4- or CCR5/CXCR4-tropic virus. CXCR4-tropic and dual-tropic (CCR5/CXCR4) HIV-1 entry is not inhibited by Selzentry.

    The efficacy of Selzentry in patients with non-CCR5-tropic HIV-1 was not demonstrated in a Phase IIb study.[1,4] In treatment-experienced patients with non-CCR5-tropic HIV-1 from baseline to Week 24, patients who received placebo demonstrated a mean decrease in HIV-1 RNA levels of 0.97 $\log_{10}$ copies/mL, compared with mean decreases of 0.91 and 1.20 $\log_{10}$ copies/mL for those who were treated with Selzentry once daily (QD) or twice daily (BID), respectively; the difference between the two groups was not statistically significant (P = 0.83 and P = 0.38, for QD and BID vs. placebo, respectively). Mean increases in CD4 cell counts were 36 cells/µL, 60 cells/µL, and 62 cells/µL, for patients who received placebo, Selzentry QD, and Selzentry BID, respectively. In patients with CXCR4 mixed or dual-tropic HIV-1, treatment with Selzentry did not demonstrate superiority to placebo and failed to demonstrate non-inferiority to placebo.[4]

127. **HIV-1 Infection Initiating Therapy with Selzentry with Unknown CCR5-Tropic Status.** Tropism testing must be conducted with a highly sensitive tropism assay that has demonstrated the ability to identify patients appropriate for Selzentry use (i.e., CCR5-tropic HIV-1).[1] DHHS and Infectious Diseases Society of America (IDSA) guidelines endorse tropism testing prior to initiation of therapy with a CCR5 antagonist (i.e., Selzentry).

128. 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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PRIOR AUTHORIZATION POLICY

POLICY: Sickle Cell Disease – Adakveo® (crizanlizumab-tmca injection, for intravenous use – Novartis)

DATE REVIEWED: 11/20/2019

OVERVIEW

Adakveo, a monoclonal antibody, is indicated to reduce the frequency of vasocclusive crises in adults and pediatric 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

157. Sickle Cell Disease. Approve Adakveo for 1 year if the patient meets the following criteria (A and B):

- **A)** The patient is ≥ 16 years of age; AND
- **B)** Adakveo is prescribed by, or in consultation with, a physician who specializes in sickle cell disease (e.g., a hematologist).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Adakveo 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.)

226. 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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PRIOR AUTHORIZATION POLICY

POLICY: Sickle Cell Disease – Endari™ (L-glutamine oral powder – Emmaus Medical, Inc)

DATE REVIEWED: 10/23/2019

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 Siklos® [hydroxyurea tablets] and 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. Because of the specialized skills required for evaluation and diagnosis of patients treated with Endari as well as the monitoring required for adverse events, approval requires Endari 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.

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. Subsequent coverage reviews for a patient who has previously met the documentation requirements and related criteria in the *ESI Endari Prior Authorization Policy* through the ESI Coverage Review Department, and who is now requesting reauthorization, the criteria utilized do NOT require resubmission of documentation for reauthorization.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indication

158. Sickle Cell Disease [documentation required]. Approve Endari for 1 year if the patient meets the following criteria (A and B):

C) The patient is ≥ 5 years of age; AND

D) Endari is prescribed by, or in consultation with, a physician who specializes in sickle cell disease (e.g., a hematologist).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Endari 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 conditions not included in the Recommended Authorization Criteria.

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

427. Endari™ oral powder [prescribing information]. Torrance CA: Emmaus Medical, Inc; July 2017.
428. 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 3, 2019.
429. Piel FB, Steinberg MH. Sickle cell disease. *N Engl J Med*. 2017;376:1561-1573.
430. The National Institutes of Health – National Heart, Lung, and Blood Institute Evidence-Based Management of Sickle Cell Disease, Expert Panel Report 2014. Available at: http://www.nhlbi.nih.gov/guidelines. Accessed on October 3, 2019.

PRIOR AUTHORIZATION POLICY

POLICY: Sickle Cell Disease – Oxbryta™ (voxelotor tablets – Global Blood Therapeutics)

DATE REVIEWED: 12/04/2019

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

159. Sickle Cell Disease. Approve Oxbryta for 1 year if the patient meets the following criteria (A and B):

E) The patient is ≥ 12 years of age; AND

F) Oxbryta is prescribed by, or in consultation with, a physician who specializes in sickle cell disease (e.g., a hematologist).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Oxbryta 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.)

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

431. Oxbryta™ [prescribing information]. San Francisco, CA: Global Blood Therapeutics; November 2019.
432. Piel FB, Steinberg MH. Sickle cell disease. *N Engl J Med*. 2017;376:1561-1573.
433. The National Institutes of Health – National Heart, Lung, and Blood Institute Evidence-Based Management of Sickle Cell Disease, Expert Panel Report 2014. Available at: http://www.nhlbi.nih.gov/guidelines. Accessed on November 18, 2019.

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:

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

434. Mycapssa capsules [prescribing information]. Needham, MA: Chiasma; April 2019.

435. 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.
436. Melmed S, Bronstein M, Chanson P, et al. A consensus statement on acromegaly therapeutic outcomes. *Natural Reviews Endocrinology.* 2018;14(9):552-561.

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

160. Meningioma. Approve for 1 year if the medication is prescribed by or in consultation with an oncologist, radiologist, or neurosurgeon.

161. Thymoma and Thymic Carcinoma. Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

162. 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:

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

437. Sandostatin® LAR Depot for injectable suspension [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; April 2019.
438. 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.
439. 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.
440. 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.
441. 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.

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:

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

442. Signifor® LAR injectable suspension [prescribing information]. Lebanon, NJ: Recordati Rare Diseases; March 2020.
443. Sharma ST, Nieman LK, Feelders RA. Cushing's syndrome: epidemiology and developments in disease management. *Clin Epidemiol*. 2015;7:281–293.
444. Tritos NA, Biller BM. Advances in medical therapies for Cushing's syndrome. *Discov Med*. 2012;13(69):171-179.
445. 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.
446. 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.

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.

163. 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

164. 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:

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
447. Somatuline® Depot injection [prescribing information]. Basking Ridge, NJ: Ipsen Biopharmaceuticals, Inc.; April 2019.
448. 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.

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:

232. 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.

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
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PRIOR AUTHORIZATION POLICY

POLICY: Spinal Muscular Atrophy – Evrysdi Prior Authorization Policy
- Evrysdi® (risdiplam oral solution – Genentech/Roche)

REVIEW DATE: 08/12/2020

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
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. 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 for use of Evrysdi 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.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

251. 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 patients who have 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 or in consultation with a physician 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, ix, and x):

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 patients who have 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 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.

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 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

ix. Medication is prescribed by or in consultation with a physician who specializes in the management of patients with spinal muscular atrophy and/or neuromuscular disorders; AND

x. According to the prescriber, the patient has responded to Evrysdi or continues to have benefit from ongoing Evrysdi therapy by an 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:

234. 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.

235. Patient has Permanent Ventilator Dependence. Data are needed to determine if this patient population with advanced spinal muscular atrophy would derive benefits from Evrysdi.

236. 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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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

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 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
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. Due to the specialized skills required for evaluation and diagnosis of patients treated with Spinraza, as well as the monitoring required for AEs and long-term efficacy, approval requires Spinraza to be prescribed by or in consultation with a physician who specializes in the condition being treated. Approvals are provided for the durations noted below. 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 and/or laboratory data. 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 resubmission of documentation for reauthorization. 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

165. 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 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 patients who have 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 or in consultation with a physician 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 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
Note: 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.

iii. For patients who have 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 by or in consultation with a physician 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 an 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:

237. Patient has Complete Paralysis of All Limbs. Data are needed to determine if this patient population would derive benefits from Spinraza.

238. Patient has Permanent Ventilator Dependence. Data are needed to determine if this patient population would derive benefits from Spinraza.

239. 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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PRIOR AUTHORIZATION POLICY

POLICY: Spinal Muscular Atrophy – Zolgensma® (onasemnogene abeparvovec-xioi suspension for intravenous infusion – AveXis)

REVIEW DATE: 06/03/2020; selected revision 08/12/2020

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 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

Table 1 (continued). Types of Spinal Muscular Atrophy.[2-5]

SMA Type	Age at Onset	Features/Clinical Presentation	Lifespan	SMN2 Copy Gene 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 $\leq$ 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

52. 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 patients who have received prior treatment with Spinraza® (nusinersen injection for intrathecal use), the prescriber attests that further therapy with Spinraza will be discontinued; AND
- **J)** For patients who have 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 or in consultation with a physician 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:

240. Patient has Four or More Survival Motor Neuron 2 (SMN2) Gene Copies. These patients were not studied and guidance does not recommend treatment.

241. 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.

242. 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.

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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PRIOR AUTHORIZATION POLICY

POLICY Synagis® (palivizumab solution for intramuscular administration – MedImmune)

APPROVAL DATE: 10/16/2019

OVERVIEW

Synagis is a humanized monoclonal antibody indicated for *prevention* of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients with at least one of the following[1]:

- bronchopulmonary dysplasia (BPD) that required medical treatment within the previous 6 months and who are ≤ 24 months of age at the beginning of the RSV season;
- history of premature birth (≤ 35 weeks gestational age) and who are ≤ 6 months of age at the beginning of the RSV season;
- hemodynamically significant congenital heart disease (CHD) who are ≤ 24 months of age at the beginning of the RSV season.

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.

Efficacy

Synagis was licensed by the FDA in June 1998, based largely on data from the IMpact-RSV trial conducted during the 1996-1997 RSV season.[2,3] IMpact-RSV enrolled children with either prematurity (≤ 35 weeks gestation and ≤ 6 months of age at the time of the study) or chronic lung disease (CLD) and ≤ 24 months of age at the time of the study. The RSV hospitalization rate was 4.8% among patients given Synagis prophylaxis, vs. 10.6% in patients given placebo. Synagis also benefits children with CHD as noted in a randomized, double-blind, placebo-controlled study of Synagis (15 mg/kg) once monthly during RSV

season in 1,287 children ≤ 2 years of age with serious CHD.[2,4] In this study, conducted from 1998 to 2002, RSV hospitalization rates were 5.3% with Synagis and 9.7% with placebo.

More recent literature has emerged to guide appropriate Synagis use.[2] Mortality from RSV-related hospitalizations has been found to be lower than previously reported. Additionally, reports have described Synagis-resistant RSV isolates from hospitalized patients who received prophylaxis. Therefore, not all infants enrolled in the two randomized trials are included in the current guidance.

Infants with CHD in Second Year of Life
A retrospective analysis of children < 3 years of age in the Tennessee Medicaid program revealed that the RSV hospitalization rate for children with CHD in the second year of life (18.2/1,000) was less than half the hospitalization rate for low-risk infants in the first 5 months after birth (44.1/1,000), a group for whom Synagis prophylaxis is not recommended.[2] Therefore, prophylaxis is not recommended during the second year of life.

Infants Born Prematurely
The New Vaccine Surveillance Network (NVSN) sponsored by the Centers for Disease Prevention and Control (CDC) was a prospective population-based surveillance program for three geographically diverse locations in the US for young children hospitalized with laboratory-confirmed RSV respiratory illness.[2] Several studies were published summarizing data from the NVSN. Data revealed that for all preterm infants (< 37 weeks' gestation), the RSV hospitalization rate was 4.6/1,000 children, which was not significantly different from the hospitalization rate for term infants, which was 5.3/1,000 children. Infants born < 29 weeks' gestation had a higher RSV hospitalization rate (19.3/1,000 children).

Infants with Anatomic Pulmonary Abnormalities or Neuromuscular Disorder
The risk for hospitalization is not well defined in children with neuromuscular disorders that impair the ability to clear secretions from the upper airway because of ineffective cough, recurrent gastroesophageal tract reflux, pulmonary malformations, tracheoesophageal fistula, upper airway conditions, or conditions requiring tracheostomy.[2] Infants with neuromuscular disease or congenital anomaly that impairs the ability to clear airway secretions from the upper airway because of ineffective cough are known to be at risk for a prolonged hospitalization related to lower respiratory tract infection and, therefore, may be considered for prophylaxis during the first year of life.

Immunocompromised Children
Risk factors for a poor outcome after RSV infection in an immunocompromised patient include age < 2 years, presence of lower respiratory tract symptoms at presentation, corticosteroid therapy, and varying degrees of lymphopenia.[2]

RSV Seasonality
The CDC National Respiratory and Enteric Virus Surveillance System (NREVSS) 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.[5] 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.[2]

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.[2] Additionally, the AAP Red Book was updated in 2018.[6] Below is a summary of their recommendations.
Groups recommended for a maximum of five monthly doses (5 months):

Infants with CLD

- Prophylaxis may be considered during the RSV season during the first year of life for preterm infants who develop CLD of prematurity defined as < 32 weeks' gestation (≤ 31 weeks, 6 days) AND required > 21% oxygen for at least the first 28 days after birth.
- In the second year of life, prophylaxis is recommended only for infants who satisfy the above definition of CLD AND who continue to require medical support (i.e., chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the 6-month period before the start of the second RSV season.

Infants with CHD

- Infants ≤ 12 months of age with hemodynamically significant CHD may benefit from prophylaxis with Synagis.
- Infants with CHD who are most likely to benefit from Synagis include: 1) infants with acynaotic heart disease who are receiving medication to control CHF and will require cardiac surgical procedures; and 2) infants with moderate to severe pulmonary hypertension. Decisions regarding prophylaxis with Synagis for infants with cyanotic heart disease may be made in consultation with a pediatric cardiologist.
- The following group of infants are not at increased RSV risk and should generally not receive prophylaxis: 1) infants and children with hemodynamically insignificant heart disease (e.g., secundum atrial septal defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta, and patent ductus arteriosus); 2) infants with lesions adequately corrected by surgery, unless they continue to require heart failure medication; 3) infants with mild cardiomyopathy who are not receiving medical therapy for the condition; and 4) children in their second year of life.
- Following cardiopulmonary bypass or at the conclusion of extracorporeal membrane oxygenation, in children who are receiving Synagis prophylaxis, a postoperative dose (15 mg/kg) should be considered for infants and children < 24 months of age.
- Children < 2 years of age who undergo cardiac transplantation during RSV season may be considered for Synagis prophylaxis.

Preterm infants born before 29 weeks' gestation (≤ 28 weeks, 6 days)

- Synagis prophylaxis may be administered to infants born ≤ 28 weeks, 6 days' gestation who are < 12 months at the start of the RSV season. For infants born during the RSV season, fewer than 5 monthly doses will be needed.

Infants with anatomic pulmonary abnormalities or a neuromuscular disease

- Infants with a congenital anomaly or neuromuscular disease that impairs the ability to clear secretions from the upper airway because of ineffective cough may be considered for Synagis prophylaxis during the first year of life.

Immunocompromised children

- Prophylaxis may be considered for children < 24 months of age who are profoundly immunocompromised during the RSV season (e.g., receiving chemotherapy, transplantation).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Synagis. All approvals are provided for up to 5 months unless otherwise noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. When referencing age, 1 year equals 12 months.

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 for those who meet the following criteria:

FDA-Approved Indications

1. **Respiratory Syncytial Virus (RSV), Prevention in an Infant with Chronic Lung Disease (CLD)**. Approve Synagis for a maximum of 5 months during the RSV season in children who meet ONE of the following conditions (A or B):
   - **A)** Infants ≤ 1 year of age at the start of the RSV season must meet the following criteria (i and ii):
     - **i.** The infant was born at < 32 weeks, 0 days gestation; AND
     - **ii.** The infant required > 21% oxygen for at least 28 days after birth; OR
   - **B)** Infants ≤ 2 years of age at the start of the RSV season must meet the following criteria (i, ii, and iii):
     - **i.** The infant was born at < 32 weeks, 0 days gestation; AND
     - **ii.** The infant required > 21% oxygen for at least 28 days after birth; AND
     - **iii.** The child 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]

2. **Respiratory Syncytial Virus (RSV), Prevention in an Infant with Congenital Heart Disease (CHD).** Approve Synagis for a maximum of 5 months during the RSV season in children who meet the following criteria (A, B, and C):
   - **A)** The infant is ≤ 1 year of age at the start of the RSV season; AND
   - **B)** According to the prescribing physician, the infant meets ONE of the following conditions (i, ii, iii, or iv):

i. The infant is considered to have hemodynamically significant cyanotic CHD; OR
ii. The infant has acyanotic heart disease AND is receiving medication to control heart failure AND will require cardiac surgical procedures; OR
iii. The infant has moderate to severe pulmonary hypertension; OR
iv. The infant has lesions that have been adequately corrected by surgery AND 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 an Infant Born Prematurely.** Approve Synagis for a maximum of 5 months during the RSV season in children who meet the following criteria (A and B):
   A) The infant is ≤ 12 months of age at the start of the RSV season; AND
   B) The infant 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 an Infant with Anatomic Pulmonary Abnormalities or a Neuromuscular Disorder.** Approve Synagis for a maximum of 5 months during the RSV season in children who meet the following criteria (A and B):
   A) The infant is ≤ 1 year of age at the start of the RSV season; AND
   B) According to the prescribing physician, the patient's condition compromises the handling of respiratory secretions.

5. **Respiraotry Syncytial Virus (RSV), Prevention in an Immunocompromised Child.** Approve Synagis for a maximum of 5 months during the RSV season in children who meet the following criteria (A, B, and C):
   A) The child is < 24 months of age at the start of the RSV season; AND
   B) Synagis is prescribed by or in consultation with an immunologist or infectious diseases specialist; AND
   C) According to the prescribing physician, the child is/will be profoundly immunocompromised during the RSV season (e.g., receiving chemotherapy, transplant).

6. **Respiratory Syncytial Virus (RSV), Prevention in a Child with Cardiac Transplant.** Approve for a maximum of 5 months during the RSV season in children who meet the following criteria (A, B, and C):

   A) The child is < 2 years of age at the start of the RSV season; AND
   B) The child 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.

   Note: Children with cardiac transplant may also be immunocompromised. In children who do not meet criteria for cardiac transplant, please see *criterion 5* above.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Synagis 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. **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Cystic Fibrosis (CF) Who Does Not Meet Any of the Approval Criteria.** The AAP guidelines for RSV note that routine use of Synagis prophylaxis in patients with CF, including neonates diagnosed with CF by newborn screening, is not recommended unless other indications are present.[6] Available studies indicate the incidence of RSV hospitalization in children with CF is uncommon and unlikely to be different from children without CF.[2] 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 Who Does Not Meet Any of the Approval Criteria.** 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., CHD, abnormalities of the respiratory tract, muscle dystonia).[2]

3. **Respiratory Syncytial Virus (RSV), Prevention in a Patient with Hematopoietic Stem Cell Transplant (Bone Marrow Transplant, Peripheral Blood, Placental, or Cord Blood) Who Does Not Meet Any of the Approval Criteria.** Phase I studies in a total of 21 patients have evaluated Synagis in BMT patients.[8] Guidelines (2009) address RSV prevention in patients with hematopoietic stem cell transplant.[9] Although a definitive, uniformly effective preemptive therapy for RSV infection among hematopoietic stem cell transplant recipients has not been identified, certain other strategies have been proposed, including systemic ribavirin, RSV antibodies (i.e., passive immunization with high RSV-titer intravenous immune globulin [IVIG], RSV immunoglobulin) in combination with aerosolized ribavirin, and RSV monoclonal antibody (e.g., Synagis). No randomized trial has been completed to test the efficacy of these strategies; therefore, no specific recommendation regarding any of these strategies can be given at this time.

4. **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]

5. **Wheezing, Prevention in a Patient Who Does Not Meet Any of the Approval Criteria.** Prophylaxis with Synagis is not recommended for primary asthma prevention or to reduce subsequent episodes of wheezing.[6]

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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PRIOR AUTHORIZATION POLICY

POLICY: Testosterone (Injectable) Products

- Depo® – Testosterone (testosterone cypionate injection – Pfizer, generics)
- Delatestryl® (testosterone enanthate injection – Actavis Pharma, Inc., generics only)
- Aveed™ (testosterone undecanoate injection – Endo Pharmaceuticals, Inc.)
- Testopel® (testosterone pellet – Endo Pharmaceuticals, Inc.)
- Xyosted™ (testosterone enanthate injection – Antares Pharma, Inc.)

APPROVAL DATE: 8/28/2019

OVERVIEW

Testosterone replacement regimens supply exogenous testosterone and restore serum testosterone levels in the normal range (300 to 1,000 ng/dL).[4] Testosterone level increases in males until 17 years of age and stabilizes to a serum level in the range of 300 to 1,000 ng/dL, until about 40 years of age. After this, the levels begin to decline at 1.2% to 2% per year. About 20% of men > 60 years of age and 50% of men > 80 years of age are estimated to have serum testosterone levels that are subnormal compared with younger men.

Male hypogonadism is characterized by low serum levels of testosterone and is classified according to the level of the hypothalamus-pituitary-testis axis involvement.[6] It is classified as primary hypogonadism when the main problem involves the testes (elevated lutenizing hormone [LH] and follicle stimulating hormone [FSH]). It is secondary hypogonadism (hypogonadotropic hypogonadism) if the hypothalamus/pituitary axis are involved; low testosterone levels in this case are associated with low or inadequately normal levels of LH and FSH. 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.[4]

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, Xyosted (testosterone enanthate) for subcutaneous [SC] use, Aveed injections for IM use, and Testopel, which is implanted subcutaneously.[1-3,7,11] These agents are all indicated in adult men for use in congenital or acquired primary hypogonadism and hypogonadotropic hypogonadism (secondary hypogonadism).[1-3,7,11] Testopel and Delatestryl (testosterone enanthate) are also indicated for delayed puberty.[2,3] The safety and efficacy of Aveed and Xyosted in males < 18 years of age have not been established.[7,11] Delatestryl (testosterone enanthate) 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. It can also be used in premenopausal women with breast cancer that have benefited from oophorectomy and are considered to have hormone-responsive tumor.

Guidelines

American Urological Association (AUA)

Guidelines from the AUA (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.[8] 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 or symptoms.

Endocrine Society

Men with Hypogonadism

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).[9]

Endocrine treatment of gender-dysphoric/gender-incongruent persons

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.[5] 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.

The World Professional Association for Transgender Health (WPATH)

The WPATH Standards of Care document (2011) states that exogenous administration of hormone therapy to induce feminizing or masculinizing changes is a medically necessary intervention for many transsexual, transgender, and gender nonconforming individuals with gender dysphoria.[10]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of injectable testosterone (e.g., testosterone cypionate, testosterone enanthate, Aveed, Testopel, Xyosted). 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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of injectable testosterone (e.g., testosterone cypionate, testosterone enanthate, Aveed, Testopel, Xyosted) is recommended in those who meet the following criteria:

FDA-Approved Indications

5. **Hypogonadism (Primary or Secondary) in Males* [Testicular Hypofunction/Low Testosterone with Symptoms].**
   - **A)** Initial Therapy. Approve for 1 year in patients with hypogonadism as confirmed by the following criteria (i, ii, and iii):
     - **i.** Patient has had persistent signs and symptoms (e.g., depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, loss of libido) of androgen deficiency (pre-treatment); AND
     - **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 for 1 year if the patient meets the following criteria (i and ii):
     - **i.** Patient has had persistent signs and symptoms (e.g., depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, loss of libido) of androgen deficiency (pre-treatment); AND
     - **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 signs and symptoms of androgen deficiency and serum testosterone levels prior to the initiation of any testosterone therapy.

6. **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.

7. **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

8. **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

Injectable testosterone (e.g., testosterone cypionate, testosterone enanthate, Aveed, Testopel) 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.)

130. To Enhance Athletic Performance. Injectable testosterone products are not recommended for approval because this indication is excluded from coverage in a typical pharmacy benefit.

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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PRIOR AUTHORIZATION POLICY

POLICY: Testosterone (Oral, Topical, and Nasal) products

Oral Testosterone Products

- Jatenzo® (testosterone undecanoate capsules – Clarus Therapeutics, Inc.)
- Striant™ (testosterone buccal system, mucoadhesive – Endo Pharmaceuticals, Inc.)

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% topical 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.)

APPROVAL DATE: 8/28/2019

OVERVIEW

The oral, topical, and nasal, and 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 is indicated:

- Primary hypogonadism (congenital or acquired) – testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchidectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations accompanied by gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.
- 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 limitations of use for these products may include that safety and efficacy in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established[1-9]; safety and efficacy in males < 18 years of age have not been established[1-10]; and topical testosterone products may have different doses, strengths or application instructions that may result in different systemic exposure[2-4,8]. The most recently labeled product Jatenzo is specifically contraindicated in men with hypogonadal conditions, such as "age-related hypogonadism", that are not associated with structural or genetic etiologies.[10] 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]

American Urological Association (AUA)

Guidelines from the AUA (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 or symptoms.

Endocrine Society

Men with Hypogonadism

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]

Endocrine treatment of gender-dysphoric/gender-incongruent persons
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.

The World Professional Association for Transgender Health (WPATH)
The WPATH Standards of Care document (2011) states that exogenous administration of hormone therapy to induce feminizing or masculinizing changes is a medically necessary intervention for many transsexual, transgender, and gender nonconforming individuals with gender dysphoria.[15]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of oral, topical, and nasal testosterone products (e.g., Jatenzo, Androderm, AndroGel, Axiron, Fortesta, Natesto, Striant, Testim, Vogelxo). 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: males are defined as individuals with the biological traits of a male, regardless of the individual's gender identity or gender expression. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of oral, topical, and nasal testosterone products (e.g., Jatenzo, Androderm, AndroGel, Axiron, Fortesta, Natesto, Striant, Vogelxo, Testim,) is recommended in those who meet the following criteria:

FDA-Approved Indications

9. Hypogonadism (Primary or Secondary) in Males* [Testicular Hypofunction/Low Testosterone with Symptoms].

A) Initial Therapy. Approve for 1 year in patients with hypogonadism as confirmed by the following criteria (i, ii, and iii):
- **i.** Patient has had persistent signs and symptoms (e.g., depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, loss of libido) of androgen deficiency (pre-treatment); AND
- **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 for 1 year if the patient meets the following criteria (i and ii):

iii. Patient has had persistent signs and symptoms (e.g., depressed mood, decreased energy, progressive decrease in muscle mass, osteoporosis, loss of libido) of androgen deficiency (pre-treatment); AND

iv. 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 signs and symptoms of androgen deficiency and serum testosterone levels prior to the initiation of any testosterone therapy.

Other Uses with Supportive Evidence

10. 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

Oral, topical, and nasal testosterone products (e.g., Jatenzo, Androderm, AndroGel, Axiron, Fortesta, Natesto, Striant, Testim, Vogelxo) 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.)

132. To Enhance Athletic Performance. Topical testosterone products are not recommended for approval because this indication is excluded from coverage in a typical pharmacy benefit.

133. 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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PRIOR AUTHORIZATION POLICY

POLICY: Thrombocytopenia – Doptelet® (avatrombopag tablets for oral use – Dova/AkaRx)

DATE REVIEWED: 03/11/2020

OVERVIEW

Doptelet, a thrombopoietin receptor agonist (TPO-RA), 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] Also, Doptelet is indicated for the treatment of thrombocytopenia in adults with chronic liver disease who are scheduled to undergo a procedure. For chronic ITP initiate at 20 mg once daily (QD) and adjust the dose to maintain a platelet count ≥ 50 x 10^9/L. Do not exceed a dose of 40 mg QD. For chronic liver disease in patients undergoing a procedure, begin Doptelet dosing 10 to 13 days before the scheduled procedure. The recommended daily dose of Doptelet is based on the patient's platelet count prior to the scheduled procedure. The dose is 60 mg (three tablets) QD for 5 days in patients with a platelet count < 40 x 10^9/L and 40 mg (two tablets) QD for 5 days for patients with a platelet count of 40 x 10^9/L to < 50 x 10^9/L. Doptelet should be given with food. Patients should undergo their procedure 5 to 8 days after the last Doptelet dose. For chronic ITP, Doptelet should be discontinued if the platelet count does not increase to ≥ 50 x 10^9/L within 4 weeks at the maximum dose of 40 mg QD. The safety and efficacy of Doptelet have not been established in pediatric patients.

Clinical Efficacy

The efficacy of Doptelet in adults with chronic ITP was assessed in a Phase III, double-blind, placebo-controlled trial in patients who had previously received one or more therapies and had an average baseline platelet count < 30 x 10^9/L.[1,2] The median exposure duration was 26 weeks for Doptelet and 6 weeks for patients given placebo. Doptelet-treated patients had a longer duration of platelet counts ≥ 50 x 10^9/L in the absence of rescue therapy compared with patients who received placebo (12.4 vs 0 weeks, respectively; P < 0.001). Also, more patients receiving Doptelet had platelet counts ≥ 50 x 10^9/L (≥ 50,000/µL) at Day 8 compared with patients who received placebo (66% vs. 0.0%, respectively; P < 0.0001).

The efficacy of Doptelet for the treatment of thrombocytopenia in patients with chronic liver disease who were scheduled to undergo a procedure was established in two identically-designed, multicenter, randomized, double-blind, placebo-controlled trials (ADAPT-1 [n = 231] and ADAPT-2 [n = 204]).[1,3] Patients were assigned to the low baseline platelet count cohort (< 40 x 10^9/L) or the high baseline platelet count cohort (≥ 40 to < 50 x 10^9/L) based on their baseline platelet count. In the trials the FDA-approved dosing was utilized for patients randomized (2:1) to receive Doptelet or placebo. Patients were scheduled to undergo their procedure (low, moderate, or high-bleeding risk) 5 to 8 days after their last treatment dose.

In ADAPT-1, patients in the low- and high-baseline platelet count groups had baseline platelet counts of 31 x 10^9/L and 44 x 10^9/L, respectively. In ADAPT-2, patients in the low- and high-baseline platelet count groups had baseline platelet counts of 32 x 10^9/L and 44 x 10^9/L, respectively. The major efficacy outcome was the proportion of patients who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure. In ADAPT-1, this endpoint was statistically superior for patients given Doptelet compared with placebo (66% for Doptelet 60 mg vs. 23% with placebo and 88% for Doptelet 40 mg vs. 38% with placebo). Also, in ADAPT-2, the endpoint was statistically superior for patients given Doptelet compared with placebo (69% for Doptelet 60 mg vs. 35% with placebo and 88% for Doptelet vs. 33% with placebo).

Guidelines
In 2019 the American Society of Hematology updated guidelines for immune thrombocytopenia.[4] 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 (IVIG), 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.

Automation: None.

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

FDA-Approved Indications

166. 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.** The patient must meet one of the following (a or b):
  - **a)** The patient has a platelet count < 30 x 10^9/L (< 30,000/µL); OR
  - **b)** The patient has a platelet count < 50 x 10^9/L (< 50,000/ µL) and according to the prescriber the patient is an increased risk of bleeding; AND
- **ii.** The patient is ≥ 18 years of age; AND
- **iii.** The agent is prescribed by or in consultation with a hematologist; AND
- **iv.** The patient meets one of the following criteria (a or b):
  - **a)** The patient has tried at least one other therapy.
    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; OR

b) The patient has undergone splenectomy; 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 (e.g., increased platelet counts); AND

ii. The patient remains at risk for bleeding complications.

167. Thrombocytopenia in Patients with Chronic Liver Disease. Approve for 5 days if the patient meets the following criteria (A, B and C):

13. The patient is an adult ≥ 18 years of age; AND

14. The patient has a current platelet count < 50 x 10^9/L (< 50,000/µL); AND

15. The patient is scheduled to undergo a procedure within 10 to 13 days after starting Doptelet therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Doptelet 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.)

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

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PRIOR AUTHORIZATION POLICY

POLICY: Thrombocytopenia – Mulpleta® (lusutrombopag tablets for oral use – Shionogi/Quotient)

DATE REVIEWED: 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 Indications

168. Thrombocytopenia in Patients with Chronic Liver Disease. Approve Mulpleta for 7 days if the patient meets the following criteria (A, B and C):
16. The patient is ≥ 18 years of age; AND
17. The patient has a current platelet count < 50 x 10^9/L (< 50,000/µL); AND
18. The patient is scheduled to undergo a procedure within 8 to 14 days after starting Mulpleta therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Mulpleta 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.)

135. 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]

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
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PRIOR AUTHORIZATION POLICY

POLICY: Thrombocytopenia – Nplate® (romiplostim injection for subcutaneous use – Amgen)

DATE REVIEWED: 03/11/2020

OVERVIEW
Nplate, a thrombopoietin receptor agonist, is indicated for the treatment of thrombocytopenia in adults with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.[1] Also, Nplate is indicated for use in 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. The initial Nplate dose is 1 mcg/kg once weekly as a subcutaneous (SC) injection by a healthcare provider. The dose should be adjusted weekly by increments of 1 mcg/kg to achieve and maintain a platelet count ≥ 50 x 10^9/L as needed to reduce the bleeding risk. Do not exceed a maximum

weekly dose of 10 mcg/kg. Discontinue Nplate if the platelet count does not increase after 4 weeks at the maximum dose.

Guidelines

ITP

In 2019 the American Society of Hematology updated guidelines for immune thrombocytopenia.[2] 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 (Nplate or Promacta® [eltrombopag tablets and oral suspension) 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 anti-D immunoglobulin, and rituximab.

Myelodysplastic Syndrome (MDS)

National Comprehensive Cancer Network recommendations regarding MDS (version 2.2020 – February 28, 2020) 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. 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 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

11. Chronic Immune Thrombocytopenia (ITP). 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.** The patient meets one of the following (a or b):
    - **a)** The patient has a platelet count < 30 x 10^9/L (< 30,000/µL); OR
    - **b)** 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; AND
  - **ii.** The agent is prescribed by or in consultation with a hematologist; AND
  - **iii.** The patient meets one of the following criteria (a or b):
    - **a)** The patient has tried at least one other therapy.
      Note: Examples of therapies are systemic corticosteroids, intravenous immunoglobulin, anti-D immunoglobulin, Promacta® (eltrombopag tablets and oral suspension), Tavalisse™

(fostamatinib disodium hexahydrate tablets), Doptelet® (avatrombopag tablets), or ritixumab; OR

b) The patient has undergone splenectomy; 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 (e.g., increased platelet counts); AND

iv. The patient remains at risk for bleeding complications.

Other Uses with Supportive Evidence

137. 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 the following criteria (i, ii, and iii):

i. The agent is prescribed by or in consultation with a hematologist or an oncologist; AND

ii. The patient has low- to intermediate-risk MDS; AND

iii. The patient meets one of the following (a or b):

a) The patient has a platelet count < 30 x 10^9/L (< 30,000/µL); OR

b) 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 for bleeding; 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 (e.g., increased platelet counts); AND

ii. The patient remains at risk for bleeding complications.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Nplate 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. 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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PRIOR AUTHORIZATION POLICY

POLICY: Thrombocytopenia – Promacta® (eltrombopag tablets and oral suspension – Novartis)

DATE REVIEWED: 03/11/2020

OVERVIEW

Promacta is also indicated for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy. Also, Promacta is indicated for use in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients ≥ 2 years of age with severe aplastic anemia. Promacta, a thrombopoietin receptor agonist, has several indications.[1] It is indicated for the treatment of thrombocytopenia in adult and pediatric patients ≥ 1 year of age with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.[1] Promacta is also indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C (CHC) to allow initiation and maintenance of interferon-based therapy. Use Promacta only in patients with CHC whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy. 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 ITP the dose of Promacta is titrated per response. 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. For the management of CHC, Promacta should be stopped upon discontinuation of antiviral treatment futility. For patients with refractory severe aplastic anemia, if no hematologic response has occurred after 16 weeks of treatment with Promacta, discontinue therapy.

Guidelines

Aplastic Anemia

Guidelines for the diagnosis and management of adult aplastic anemia are also available for the British Society.[2] The current standard first-line immunosuppressive therapy is horse ATG (ATG-ATGAM) combined with cyclosporine. 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. 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).

ITP
In 2019 the American Society of Hematology updated guidelines for immune thrombocytopenia.[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 (IVIG), anti-D immunoglobulin, and rituximab.

Myelodysplastic Syndrome (MDS)
Current recommendations from the NCCN for MDS (version 2.2020 – February 28, 2020) 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. Of note, data are 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 Indication

12. Aplastic Anemia. Approve Promacta for 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.** The patient has low platelet counts at baseline (pretreatment) [e.g., < 30 x 10^9/L {< 30,000/µL}; AND
  - **ii.** Promacta is prescribed by, or in consultation with, a hematologist; AND
  - **iii.** The patient meets one of the following (a or b):
    - **a)** The patient had tried at least one immunosuppressant therapy.
      Note: Examples of therapies are cyclosporine, Atgam® (lymphocyte immune globulin, anti-thymocyte globulin [equine] sterile solution for intravenous use only), mycophenolate moefetil, or sirolimus; OR
    - **b)** The patient will be using Promacta in combination with standard immunosuppressive therapy.
      Note: Examples of therapies are cyclosporine, Atgam® (lymphocyte immune globulin, anti-thymocyte globulin [equine] sterile solution for intravenous use only), mycophenolate moefetil, or sirolimus; 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.

13. Chronic Immune Thrombocytopenia. Approve Promacta if the patient meets one the following (A or B):

A. Initial Therapy. Approve for 3 months if the patient meets all the following criteria (i, ii and iii):
- **i.** The patient meets one of the following (a or b):
  - **a)** The patient has a platelet count < 30 x 10^9/L (< 30,000/µL); OR
  - **b)** 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 for bleeding; AND
- **ii.** The agent is prescribed by, or in consultation with, a hematologist; AND
- **iii.** The patient meets ONE of the following criteria (a or b):
  - **a)** The patient has tried at least one other therapy.
    Note: Examples of therapies are systemic corticosteroids, intravenous immunoglobulin, anti-D immunoglobulin, Nplate® (romiplostim injection for subcutaneous use), Tavalisse™ (fostamatinib disodium hexahydrate tablets), Doptelet® (avatrombopag tablets), or rituximab; OR
  - **b)** The patient has undergone splenectomy; 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 (e.g., increased platelet counts); AND
- **ii.** The patient remains at risk for bleeding complications.

14. Treatment of Thrombocytopenia in Patients with Chronic Hepatitis C. Approve Promacta for 1 year if the patient meets the following criteria (A, B, and C):

A) Promacta is prescribed by, or in consultation with, either a gastroenterologist, a hepatologist, or a physician that specializes in infectious disease; AND

B) The patient has low platelet counts at baseline (pretreatment) [e.g., < 75 x 10^9/L {< 75,000/µL}]; AND

C) The patient will be receiving interferon-based therapy for chronic hepatitis C.
Note: Examples of therapies are pegylated interferon (Pegasys® [peginterferon alfa-2a injection], PegIntron® [peginterferon alfa-2b injection], or Intron A® (interferon alfa-2b).

Other Uses with Supportive Evidence

138. Thrombocytopenia in Myelodysplastic Syndrome (MDS). 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. The agent is prescribed by, or in consultation with, a hematologist or an oncologist; AND
- b. The patient has low- to intermediate-risk MDS; AND
- c. The patient meets one of the following (a or b):
  - **c)** The patient has a platelet count < 30 x 10^9/L (< 30,000/µL); OR
  - **d)** 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 for bleeding; 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 (e.g., increased platelet counts); AND
iv. The patient remains at risk for bleeding complications.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Promacta 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. 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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PRIOR AUTHORIZATION POLICY

POLICY: Thrombocytopenia – Tavalisse™ (fostamatinib disodium hexahydrate tablets – Rigel/Patheon Whitby)

DATE REVIEWED: 03/11/2020

OVERVIEW

Tavalisse, a tyrosine kinase inhibitor with demonstrated activity against spleen tyrosine kinase, is indicated for the treatment of thrombocytopenia in adult patients 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.

Clinical Efficacy

The efficacy of Tavalisse was established in two identical, double-blind, placebo-controlled, multinational, randomized (2:1), 24-week studies (FIT-1 and FIT-2) in patients with persistent or chronic ITP with an insufficient response to previous therapies.[1,2] An open-label extension trial (FIT-3), involving patients from FIT-1 and FIT-2 was also performed.[1,3] In FIT-1 (n = 76), a stable platelet response (defined as at least 50 x 10^9/L on at least four of the six visits between Weeks 14 to 24) was achieved in 18% of patients (n = 9/51) who received Tavalisse compared with none of the patients who received placebo (P = 0.03).[1,2] In FIT-2 (n = 74), a stable platelet response was achieved in 16% of patients (n = 8/50) given Tavalisse vs. 4% of patients (n = 1/24) given placebo (a non statistically-significant difference). In FIT-1 and FIT-2, 47 patients given Tavalisse had received a prior thrombopoietin receptor agonist TPO-RA therapy, of which 17% of patients (n = 8/47) achieved a stable response. In FIT-3 (n = 123), 50% of the patients (n = 61/123) discontinued early. Of the 44 patients treated with placebo in the prior study, 23% of patients (n = 10/44) met the criteria for a stable response.

Guidelines

In 2019 the American Society of Hematology updated guidelines for immune thrombocytopenia.[4] 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 (IVIG), 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 event 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 Indications

169. Chronic Immune Thrombocytopenia. Approve for if the patient meets one of the following criteria (A or B):

19. Initial Therapy. Approve for 3 months if the patient meets all of the following criteria (i, ii, iii, and iv):

i. The patient meets one of the following (a or b):

a) The patient has a platelet count < 30 x 10^9/L (< 30,000/µL): OR

b) 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; AND

ii. The patient is ≥ 18 years of age; AND

iii. The agent is prescribed by or in consultation with a hematologist; AND

iv. The patient meets one of the following criteria (a or b):

a) The patient has tried at least one other therapy.
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; OR

b) The patient has undergone splenectomy; OR

C. 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 (e.g., increased platelet counts); AND

iv. The patient remains at risk for bleeding complications.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Tavalisse 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.

139. 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]).[5,6] Many other therapies are available for this use.

140. Rheumatoid Arthritis. Tavalisse has been studied in patients with rheumatoid arthritis.[7-11] However, other therapies are more well-established and are recommended in guidelines.

141. 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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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

170. Autosomal Dominant Polycystic Kidney Disease. Approve for 1 year if the patient meets the following criteria (A, B, C and D):

20. The patient is ≥ 18 years of age; AND

21. The agent is prescribed by or after consultation with a nephrologist; AND

22. 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

23. 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.

142. 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.

143. 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.

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

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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

15. 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.)

145. **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.

146. **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.

147. **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]

148. 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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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

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PRIOR AUTHORIZATION POLICY

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.)

149. Erythema Caused by Conditions Other Than Rosacea.

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

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574. Del Rosso JQ, Thiboutot D, Gallo R, et al. Consensus recommendations from the American Acne & Rosacea Society on the management of rosacea, part 2: a status report on topical agents. *Cutis*. 2013;92(6):277-284.
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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

16. **Actinic Keratoses.** Approve for 6 months.

Other Uses with Supportive Evidence

17. **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:

151. 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.

152. 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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PRIOR AUTHORIZATION POLICY

POLICY: Topical Retinoids – Aklief® – (trifarotene cream – Galderma Laboratories)

DATE REVIEWED: 12/04/2019

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. Use should be limited to the treatment of medical conditions, and prescription benefit coverage is not recommended for cosmetic conditions. All approvals are provided for the duration noted below

Automation: None

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indication

18. Acne Vulgaris. Approve for 3 years.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Aklief 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.)

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

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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.

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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.

REFERENCES

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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

19. Acne Vulgaris. Approve for 3 years.

Other Uses with Supportive Evidence

~~20.~~ 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:

154. 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.

155. 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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PRIOR AUTHORIZATION POLICY

POLICY: Uplizna Prior Authorization Policy

- Uplizna™ (inebilizumab-cdon injection for intravenous use – Viela Bio)

REVIEW DATE: 06/24/2020

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 for intravenous use), a complement inhibitor, is the only other FDA-approved medication for treatment of NMOSD in adult patients who are anti-aquaporin-4 antibody positive.[4] For acute attacks, typical treatment is high-dose intravenous corticosteroids.[5,6] 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 by providers 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

171. Neuromyelitis Optica Spectrum Disorder. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **C)** Patient is ≥ 18 years of age; AND
- **D)** Neuromyelitis optica spectrum disorder diagnosis was confirmed by blood serum test for anti-aquaporin-4 antibody positive; AND
- **E)** Patient has previously tried one of the following systemic therapies (i, ii, iii, iv, or v):
  - **i.** Azathioprine
  - **ii.** Corticosteroid
  - **iii.** Mycophenolate mofetil
  - **iv.** Rituximab
  - **v.** Soliris (eculizumab for intravenous use)
- **F)** Uplizna 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:

244. 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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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

252. 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.

253. 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.)

156. 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]

157. 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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PRIOR AUTHORIZATION POLICY

POLICY: Vesicular Monoamine Transporter Type 2 Inhibitors – Austedo® (deutetrabenazine tablets – Teva)

DATE REVIEWED: 06/10/2020

OVERVIEW

Austedo reversibly depletes monoamines (such as dopamine, serotonin, norepinephrine, and histamine) from nerve terminals.[1] Austedo and its major circulating metabolites (α-dihydrotetrabenazine [HTBZ] and β-HTBZ) reversibly inhibit vesicular monoamine transporter type 2 (VMAT2), resulting in decreased uptake of monoamines (e.g., dopamine) into synaptic vesicles and depletion of monoamine stores. Austedo is indicated for the treatment of chorea associated with Huntington's disease and for the treatment of tardive dyskinesia in adults. Austedo has been evaluated for use in one small, Phase Ib study in adolescents with moderate-to-severe tics associated with Tourette syndrome.[2] Tetrabenazine (Xenazine®, generics) is also a VMAT2 inhibitor indicated for the treatment of chorea associated with HD.[3]

Guidelines

According to the American Academy of Neurology (AAN) guidelines on the treatment of chorea of Huntington's disease (2012), if HD 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.[5] Austedo is not addressed in the guidelines.

Safety

Austedo is contraindicated in patients who are suicidal or in patients with untreated or inadequately treated depression in patients with Huntington's disease.[1] Austedo also has a Boxed Warning regarding depression and suicidality in patients with Huntington's disease. Patients with Huntington's disease are at increased risk for depression, and suicidal ideation or behaviors (suicidality), and Austedo may increase the risk for suicidality in patients with Huntington's disease. When considering the use of Austedo, the risk of

suicidality should be balanced against the need for treatment of chorea. All patients treated with Austedo should be observed for new or worsening depression or suicidality. If depression or suicidality does not resolve, consider discontinuing treatment with Austedo.

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 1 year in duration.

Documentation: In the Austedo Policy, 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 Austedo is recommended in those who meet the following criteria:

FDA-Approved Indications

21. **Chorea Associated with Huntington's Disease:** Approve for 1 year if the patient meets BOTH of the following criteria (A and B):
    - **A)** Patient has been diagnosed with chorea associated with Huntington's Disease **[documentation required]**; AND
    - **B)** Austedo is prescribed by or in consultation with a neurologist.

22. **Tardive dyskinesia:** Approve for 1 year if Austedo is prescribed by or in consultation with a neurologist or psychiatrist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Austedo 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.)

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

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603. Xenazine® tablets [prescribing information]. Deerfield, IL: Lundbeck; September 2017.
604. 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.

OTHER REFERENCES UTILIZED

- 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.

PRIOR AUTHORIZATION POLICY

POLICY: Vesicular Monoamine Transporter Type 2 Inhibitors – Ingrezza® (valbenazine capsules)

DATE REVIEWED: 06/10/2020

OVERVIEW

Ingrezza, a vesicular monoamine transporter type 2 (VMAT2) inhibitor, is indicated for the treatment of adults with tardive dyskinesia.[1] Ingrezza is thought to provide benefit in tardive dyskinesia through the reversible inhibition of VMAT2, a transporter that regulates monoamine (e.g., dopamine) uptake from the cytoplasm to the synaptic vesicle for storage and release, thereby reducing presynaptic release of dopamine. The initial dose is 40 mg once daily (QD) taken with or without food. After one week, increase to the recommended dose of 80 mg QD. Continuation of 40 mg QD dosing may be considered for some patients.

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 1 year in duration.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

2. Tardive Dyskinesia. Approve for 1 year if Ingrezza is prescribed by or in consultation with a neurologist or psychiatrist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Ingrezza 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.)

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
605. Ingrezza® capsules [prescribing information]. San Diego, CA: Neurocrine Biosciences, Inc.; April 2020.

OTHER REFERENCES UTILIZED
- 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.

PRIOR AUTHORIZATION POLICY

POLICY: Vesicular Monoamine Transporter Type 2 Inhibitors – Tetrabenazine tablets (Xenazine® – Lundbeck, generics)

DATE REVIEWED: 06/10/2020

OVERVIEW
Tetrabenazine reversibly depletes monoamines (such as dopamine, serotonin, norepinephrine, and histamine) from nerve terminals.[1] Tetrabenazine, and its major circulating metabolites (α-dihydrotetrabenazine [HTBZ] and β-HTBZ), reversibly inhibits vesicular monoamine transporter type 2 (VMAT2), resulting in decreased uptake of monoamines into synaptic vesicles and depletion of monoamine stores. Tetrabenazine is indicated for the treatment of chorea associated with Huntington's disease (HD). There are several other published studies which have assessed the efficacy and safety of tetrabenazine for the treatment of other hyperkinetic movement disorders (e.g., tics in Tourette Syndrome and tardive dyskinesia).

Beginning in September 2015, tetrabenazine has been available as an AB-rated generic to brand Xenazine. Generic tetrabenazine is Food and Drug Administration (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 HD (2012) states that if chorea in HD 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.

Safety

The prescribing information for tetrabenazine includes a contraindication in patients who are actively suicidal or who have depression which is untreated or undertreated.[1] Of note, tetrabenazine is only FDA-approved for use in patients with Huntington's disease. Tetrabenazine also has a Boxed Warning regarding depression and suicidality in patients with Huntington's disease. Patients with Huntington's disease are at increased risk for depression and suicidal ideation or behaviors (suicidality), and tetrabenazine may increase the risk for suicidality in these patients. When considering the use of tetrabenazine, the risk of suicidality should be balanced against the need for treatment of chorea. All patients treated with tetrabenazine should be observed for new or worsening depression or suicidality. If depression or suicidality does not resolve, consider discontinuing treatment with tetrabenazine.

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

23. Chorea Associated with Huntington's Disease. Approve for 1 year if tetrabenazine is prescribed by or in consultation with a neurologist.

Other Uses with Supportive Evidence

3. Hyperkinetic Dystonia. Approve for 1 year if tetrabenazine is prescribed by or in consultation with a neurologist.

4. Tardive Dyskinesia. Approve for 1 year if tetrabenazine is prescribed by or in consultation with a neurologist or psychiatrist.

5. **Tourette Syndrome and Related Tic Disorders.** Approve for 1 year if tetrabenazine is prescribed by or in consultation with a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Tetrabenazine 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.)

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

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626. Guay DR. Tetrabenazine, a monoamine-depleting drug used in the treatment of hyperkinetic movement disorders. *Am J Geriatr Pharmacother*. 2010;8(4):331-373.
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PRIOR AUTHORIZATION POLICY

POLICY: Wakefulness-Promoting Agents – Armodafinil, Modafinil

- Nuvigil® (armodafinil tablets – Cephalon, generics)

- Provigil® (modafinil tablets – Cephalon, generics)

DATE REVIEWED: 08/21/2019; selected revision 03/25/2020 and 5/20/2020

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 excessive sleepiness associated with narcolepsy; obstructive sleep apnea/hypoapnea syndrome (approved as adjunctive therapy); and shift work sleep disorder.[1,2] Armodafinil and modafinil are Schedule IV controlled substances. 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.

Guidelines

According to the American Academy of Sleep Medicine, 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 SSRIs, 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.

Guidelines from the AASM, updated in 2007, state that modafinil may be effective for the treatment of daytime sleepiness due to PD.[14] A practice parameter on the treatment of nonmotor symptoms of PD, published by the American Academy of Neurology (AAN) in 2011, states that for patients with PD and excessive daytime sleepiness (EDS), modafinil is effective in improving patients' perception of wakefulness, but is ineffective in objectively improving EDS as measured by objective tests.[17] The practice parameter recommendations indicate modafinil should be considered for patients to improve their subjective perception of EDS; however, it should be noted that patients may experience an improvement in sleep perception without an actual improvement in objective sleep measurements. While armodafinil has not been studied for this use, expert opinion considers it to be interchangeable with modafinil for this condition.

Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin, updated in 2007 by the AASM, state that modafinil may be effective for the treatment of daytime sleepiness due to MS.[14] Although the results with modafinil in clinical trials are heterogeneous, expert opinion considers it to be a first-line anti-fatigue drug for MS 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.[29-32] The 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 idiopathic hypersomnia.[14] As there may be underlying causes/behaviors associated with EDS, 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 1 year in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nuvigil (brand and generic) and Provigil (brand and generic) are recommended in those who meet one of the following criteria:

Food and Drug Administration (FDA)-Approved Indications

25. 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)** The patient is ≥ 18 years of age; AND
- **B)** The patient meets one of the following criteria (i or ii):
  - **i.** Armodafinil/modafinil will be used in conjunction with continuous positive airway pressure (CPAP); OR
  - **ii.** The patient is unable to initiate or tolerate CPAP therapy; AND
- **C)** If brand Provigil or Nuvigil is being requested, the patient meets both of the following criteria (i and ii):
  - **i.** The patient has tried generic modafinil or generic armodafinil; AND
  - **ii.** The 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.

26. Excessive Sleepiness Associated with Shift Work Sleep Disorder. 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 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.** The patient has tried generic modafinil or generic armodafinil; AND
  - **ii.** The 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.

27. Excessive Daytime Sleepiness Associated with Narcolepsy. Approve for 1 year if the patient meets both of the following criteria (A, B and C):
- **A)** The patient is ≥ 18 years of age; AND
- **B)** Narcolepsy has been confirmed with polysomnography and a multiple sleep latency test (MSLT); AND
- **C)** If brand Provigil or Nuvigil is being requested, the patient meets both of the following criteria (i and ii):
  - **i.** The patient has tried generic modafinil or generic armodafinil; AND
  - **ii.** The 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

~~28.~~ Adjunctive/Augmentation Treatment for Depression in Adults. 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 is concurrently receiving other medication therapy for depression (e.g., selective serotonin reuptake inhibitors [SSRIs]); AND
- **C)** If brand Provigil or Nuvigil is being requested, the patient meets both of the following criteria (i and ii):
  - **i.** The patient has tried generic modafinil or generic armodafinil; AND
  - **ii.** The 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 Myotonic Dystrophy. Approve for 1 year if the patient meets both of the following criteria (A and B):
- **A)** The 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.** The patient has tried generic modafinil or generic armodafinil; AND
  - **ii.** The 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.

~~30.~~ 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)** The 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.** The patient has tried generic modafinil or generic armodafinil; AND
  - **ii.** The 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.~~ **Fatigue Associated with Multiple Sclerosis (MS).** Approve for 1 year if the patient meets both of the following criteria (A and B):
- **A)** The 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.** The patient has tried generic modafinil or generic armodafinil; AND
  - **ii.** The 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.~~ **Idiopathic Hypersomnia.** Approve for 1 year if the patient meets both of the following (A, B and C):
- ~~a)~~ The 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.** The patient has tried generic modafinil or generic armodafinil; AND
  - **ii.** The 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

Nuvigil and Provigil (brand and generic) 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.)

12. **Attention Deficit Hyperactivity Disorder (ADHD).** The American Academy of Pediatrics (AAP) clinical practice guidelines for the treatment of ADHD in children and adolescents (2011) does not address the use of modafinil/armodafinil.[43,44] 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 adult patients with ADHD, preliminarily suggested that modafinil may be useful for this condition.[45,49] 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.[47] 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.

13. **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.[48-50] In one study (n = 257) armodafinil was not more effective than placebo in treating bipolar depression.[51] Only limited data supports modafinil for this condition and more data are needed.

14. **Cancer-Related Fatigue.** The National Comprehensive Cancer Network (NCCN) guidelines on cancer-related fatigue (version 1.2019 – March 12, 2019) no longer consider modafinil to be effective for the treatment of cancer-related fatigue and recommend against its use.[28] 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.[7] Other studies do not support the use of modafinil or armodafinil for cancer-related fatigue.[69-72]

15. **Chronic Fatigue Syndrome.** Limited data characterize modafinil therapy in those with chronic fatigue syndrome.[52,53] 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.[70] More data are required to assess efficacy in this patient population.

16. **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.[54]

17. **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).[55-58] Further studies are needed before its use in the general population in these types of situations can be promoted.

18. **Fatigue and Excessive Daytime Sleepiness in Chronic Traumatic Brain Injury (TBI).** A single-center, double-blind, placebo- controlled, crossover trial involving 53 patients suggests that overall, modafinil was not beneficial in relieving fatigue and EDS in such patients.[59] In a small (n = 20) randomized, placebo-controlled trial, modafinil improved EDS vs. placebo in patients with TBI; however, modafinil did not improve fatigue compared with placebo.[60] Additional data are needed to determine effectiveness in this setting.

19. **Fibromyalgia.** Limited data are available regarding the use of modafinil in fibromyalgia with most of the data being observational.[61-63] 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.

20. **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.

21. **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 EDS. Very limited data (i.e., case reports and one small study) have explored the use of modafinil in

these patients to improve alertness.[64,73] More data are needed to determine effectiveness in this condition.

22. 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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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

33. 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.

254. 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:

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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PRIOR AUTHORIZATION POLICY WITH STEP THERAPY

POLICY: Wakefulness-Promoting Agents – Wakix® (pitolisant tablets – Harmony)

DATE REVIEWED: 10/02/2019; selected revision 03/25/2020

OVERVIEW

Wakix is indicated for the treatment of excessive daytime sleepiness (EDS) in adults with narcolepsy.[1] Wakix is an antagonist/inverse agonist of the histamine-3 (H_3) receptor. 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 adult patients with excessive sleepiness associated with narcolepsy, 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 adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (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]

Disease Overview

Narcolepsy is a rare, chronic neurologic disorder that affects the brain's ability to control sleep-wake cycles.[7] 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. The most typical symptoms are excessive daytime sleepiness, cataplexy, sleep paralysis, and hallucinations. 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.

Guidelines

The American Academy of Sleep Medicine (AASM) published practice parameters in 2007 for the treatment of narcolepsy 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.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Wakix. 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 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

34. Excessive Daytime Sleepiness Associated with Narcolepsy. Approve for 1 year if the patient meets one of the following criterion (A, B, and C):
- **a)** The patient is ≥ 18 years of age; AND
- **b)** Narcolepsy has been confirmed with polysomnography and a multiple sleep latency test (MSLT); AND
- **c)** The patient meets one of the following criteria (i or ii):
  - **i.** The 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. The 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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Wakix 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.)

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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PRIOR AUTHORIZATION POLICY

POLICY: Weight Loss Drugs

- 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)

DATE REVIEWED: 10/30/2019; selected revisions 03/11/2020

OVERVIEW

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). Appetite suppressant products currently available are as follows:

- benzphetamine hydrochloride (Regimex and generic products) C-III [noradrenergic][5,32]
- diethylpropion hydrochloride (generic products) C-IV [noradrenergic][6]
- phendimetrazine tartrate (generic products) C-III [noradrenergic][7]
- phentermine hydrochloride (Adipex-P, Lomaira, and generic products) C-IV [noradrenergic][8-9,31]
- Qsymia (anorectic and antiepileptic) C-IV[10]
- Contrave (opioid antagonist and antidepressant)[27]
- Saxenda (glucagon-like peptide-1 agonist)[28]

The other commercially available weight loss product, orlistat, acts by inhibiting the absorption of dietary fats and is not an appetite suppressant.[11] Orlistat is available by prescription as Xenical, and over-the-counter (OTC) as Alli® (orlistat 60 mg capsules). Alli is not included within the scope of this policy.

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 BMI of ≥ 30 kg/m^2 who have not responded to a weight reducing regimen (diet and/or exercise) alone.[5-7,32] 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).[8-9,31] Qsymia, Contrave, and Saxenda 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).[10,27-28]

Xenical

Xenical is indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced calorie diet.[11] Xenical is also indicated to reduce the risk for weight regain after prior weight loss. Xenical is indicated for obese patients with an initial BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 in the presence of other risk factors (e.g., hypertension, diabetes, dyslipidemia).[11] Xenical has been used effectively to further reduce weight, maintain weight loss, or prevent as much regain in patients (BMI

initially 28 to 43 kg/m^2) who initially lost weight on a 6-month low calorie diet.[12] In another study, patients who lost ≥ 5% of their body weight on an 8-week very-low-calorie diet (n = 309) were randomized to receive Xenical or placebo for 3 years, plus lifestyle counseling.[13] The mean weight gain after 3 years was 4.6 kg with Xenical and 7.0 kg with placebo (P < 0.02). The incidence of new cases of type 2 diabetes was reduced in the Xenical group (n = 8/153) vs. placebo (n = 17/156) [P = 0.04].

The XENical in the prevention of Diabetes in Obese Subjects (XENDOS) study was a 4-year, double-blind, prospective trial that randomized 3,305 patients to lifestyle changes plus either Xenical 120 mg TID with meals or placebo.[14] The primary study outcomes were the onset of type 2 diabetes and body weight changes. Patients (30 to 60 years of age) were nondiabetic and had a BMI ≥ 30 kg/m^2. Most patients had normal glucose tolerance, but some had impaired glucose tolerance (79% and 21% of patients, respectively). Lifestyle changes and a reduced calorie diet were also implemented. Of the patients randomized to Xenical, 52% completed 4 years of treatment vs. 34% of patients randomized to placebo. The mean weight loss with Xenical at 4 years was greater (5.8 kg) compared with placebo (3.0 kg; P < 0.001). After 4 years of therapy, fewer patients randomized to Xenical progressed to having type 2 diabetes compared with placebo (P = 0.0032) [cumulative 4-year incidence rates of 6.2% {Xenical} and 9.0% {placebo}] (risk reduction of 37.3%). The reduction in the development of type 2 diabetes with Xenical was more marked in patients with impaired glucose tolerance at baseline (18.8% with Xenical vs. 28.8% with placebo) corresponding to a 45% risk reduction. Xenical did not reduce the risk of developing diabetes in patients with normal glucose tolerance at baseline.[13] The effect of Xenical to delay the onset of type 2 diabetes in obese patients with impaired glucose tolerance is presumably due to weight loss and not to an independent effect(s) of the drug on glucose or insulin metabolism.

Use of Xenical in Obese or Overweight Pediatric Patients

In a 54-week trial, 539 adolescents (12 to 16 years of age with BMI ≥ 2 units above the 95th percentile; maximum BMI of 44 kg/m^2) were randomized to Xenical 120 mg TID or placebo.[11,15] Both groups were on a mildly hypocaloric diet, exercise and behavioral therapy. In all, 190 patients dropped out. Both groups had a decrease in BMI up to 12 weeks. At 54 weeks, the mean BMI decreased from baseline by -0.55 kg/m^2 with Xenical and increased by +0.31 kg/m^2 with placebo (P = 0.001); weight increased by +0.53 kg with Xenical and by +3.14 kg with placebo (P < 0.001). In a 6-month double-blind trial, 40 adolescents (14 to 18 years of age) were randomized to Xenical 120 mg TID (mean BMI 39.2 kg/m^2) or placebo (mean BMI 41.7 kg/m^2).[16] Patients received dietary and exercise counseling. No statistically significant difference was noted between the two study groups for decrease in BMI from baseline to 6 months (P = 0.39), the primary end point. The BMI decreased within the Xenical group (-1.3 ± 1.6 kg/m^2; P = 0.04) and within the placebo group (-0.8 ± 3.0 kg/m^2; P = 0.02) which was statistically significant. The Xenical group had increased adverse events compared to placebo, primarily gastrointestinal symptoms.

The most commonly used pharmacotherapeutic agents in pediatric patients are sibutramine (prior to withdrawal from the US market), orlistat, and metformin (note that metformin is not indicated for the treatment of obesity).[17] A meta-analysis, commissioned by the Endocrine Society task force, showed that sibutramine demonstrated the greatest effect with a decrease in BMI of -2.4 kg/m^2 (95% confidence interval [CI]: 1.8, 3.1 kg/m^2) after 6 months, but patients had a greater increase in blood pressure and pulse rate than with placebo.[20] Orlistat produced a significant decrease in BMI of -0.7 kg/m^2 (95% CI: 0.3, 1.2 mg/m^2) but there were increased gastrointestinal adverse events (abdominal discomfort, pain, and steatorrhea). Orlistat has reduced utility in children since it must be taken with each meal and children are often in school at lunchtime.[17] Metformin monotherapy decreased BMI in hyperinsulinemic, non-diabetic obese adolescents slightly but significantly in each of the studies analyzed. The overall effect did not reach statistical significance in the meta-analysis. Metformin is indicated for type 2 diabetes mellitus in children ≥ 10 years of age. The Endocrine Society guidelines recommend that use of agents that are not indicated for obesity

(e.g., metformin, octreotide, leptin, topiramate, growth hormone) should be restricted to large, well-controlled studies.

Guidelines

The Endocrine Society published a clinical practice guideline (2015) for the pharmacological management of obesity.[29] 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.

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.[30] 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.[17] 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.[17] The Centers for Disease Control (CDC) derived normative percentiles are recommended as the appropriate method for determining the BMI in children.[18-19]

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.

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 Adults or Adolescents ≥ 16 Years of Age. Note: For individuals who have not completed the initial 3 months of therapy, criterion 1, A 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 risk factors besides obesity (e.g., diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea) [Appendix A contains a BMI chart]; AND
- **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) Patients 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 risk factors besides obesity (e.g., diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea); AND
- **ii.** Patient is currently engaged in behavioral modification and on a reduced calorie diet; AND
- **iii.** Patient has lost ≥ 5% of baseline body weight.

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.[29] According to prescribing information, safety and efficacy have not been established for diethylpropion and phentermine (hydrochloride or resin) in children younger than 16 years,[6,8,9,31] and for benzphetamine, phendimetrazine and Xenical in children < 12 years of age.[5,7,11,32] However, the Endocrine Society has established guidelines for use of Xenical in pediatric patients.[17] Benzphetamine, diethylpropion, phendimetrazine and phentermine are not included in these guidelines.

II. Coverage of Contrave is recommended in those who meet all of the following criteria:

FDA-Approved Indications

1. Weight Loss in Adults ≥ 18 Years of Age. Note: For individuals who have not completed the initial 4 months of therapy, criterion 1, A 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 ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 for those with risk factors besides obesity (e.g., diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea) [Appendix A contains a BMI chart]; AND

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) Patients 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 risk factors besides obesity (e.g., diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea); AND
ii. Patient is currently engaged in behavioral modification and on a reduced calorie diet; AND
iii. Patient has lost ≥ 5% of baseline body weight.

The recommended maintenance dose of Contrave is achieved at Week 4.[27] 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.

III. Coverage of Qsymia is recommended in those who meet all of the following criteria:

FDA-Approved Indications

1. **Weight Loss in Adults ≥ 18 Years of Age.** Note: For individuals who have not completed the initial 6 months of therapy, criterion 1, A 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 risk factors besides obesity (e.g., diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea) [Appendix A contains a BMI chart]; AND
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) Patients 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 risk factors besides obesity (e.g., diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea); AND
ii. Patient is currently engaged in behavioral modification and on a reduced calorie diet; AND
iii. Patient has lost ≥ 5% of baseline body weight.

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.

IV. Coverage of Saxenda is recommended in those who meet all of the following criteria:

1. **Weight Loss in Adults ≥ 18 years of Age.** Note: For individuals who have not completed the initial 4 months of therapy, criterion 1, A 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 risk factors besides obesity (e.g., diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea) [Appendix A contains a BMI chart]; AND
     - **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)** Patients 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 risk factors besides obesity (e.g., diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea); AND
     - **ii.** Patient is currently engaged in behavioral modification and on a reduced calorie diet; AND
     - **iii.** Patient has lost ≥ 4% of baseline body weight.

   The change in body weight with Saxenda should be evaluated 16 weeks after initiating Saxenda.[28] 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.

V. Coverage of Xenical is recommended in those who meet all of the following criteria:

FDA-Approved Indications

1. **Weight Loss in Adults ≥ 18 Years of Age**. Note: For individuals who have not completed the initial 3 months of therapy, criterion 1, A 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 risk factors besides obesity (e.g., diabetes, dyslipidemia, hypertension, coronary heart disease, sleep apnea) [Appendix A contains a BMI chart]; OR
       - **b)** Patient had an initial BMI ≥ 30 kg/m^2, or a BMI ≥ 27 kg/m^2 for those with risk factors besides obesity (e.g., diabetes, dyslipidemia, hypertension, coronary heart disease, sleep apnea) if maintaining weight loss after using a low calorie diet; AND
     - **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)** Patients 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 risk factors besides obesity (e.g., diabetes mellitus, impaired glucose tolerance, dyslipidemia, hypertension, coronary heart disease, sleep apnea); AND
     - **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 Adolescents Aged ≥ 12 to < 18 Years.** Note: For individuals who have not completed the initial 3 months of therapy, criterion 2, A 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 severe co-morbidity (type 2 diabetes mellitus, premature cardiovascular disease) or has a strong family history of type 2 diabetes or premature cardiovascular disease (CVD); AND
     - **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 co-morbidities; AND
     - **iii.** Patient is currently engaged in behavioral modification and on a reduced calorie diet.
   - **B)** Patients 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 severe co-morbidity (type 2 diabetes or premature CVD) or strong family history of type 2 diabetes or premature CVD; AND
     - **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

These drugs for weight loss 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. **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.[5-10,27-28,31-32] A 12-week, pilot study assessed the addition of phentermine to Saxenda following 1 year of Saxenda treatment.[34] 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).[21]

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.[22-23] In an open-label study, 10 patients with binge eating disorder were treated with Qsymia.[35] 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.[18] 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.[24] 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.[36] 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.[37] 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.[25]

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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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® (collagenase clostridium histolyticum for intralesional injection – Endo Pharmaceuticals)

DATE REVIEWED: 01/29/2020

OVERVIEW

Xiaflex is a combination of bacterial collagenases indicated for the treatment of adult patients with Dupuytren's contracture with a palpable cord, and for the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.[1]

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 (MP) joint or 20 degrees to 80 degrees in a proximal interphalangeal (PIP) 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). In the pivotal studies, patients were required to have a penile deformity of at least 30 degrees.[1]

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 MP or PIP 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 administered by a healthcare provider with expertise in the condition being treated.

Prior authorization is 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 in patients meeting all of the following criteria (A, B, C, and D):
- **A)** The patient is ≥ 18 years of age; AND
- **B)** At baseline (prior to initial injection of Xiaflex), the patient had contracture of a metacarpophalangeal (MP) or proximal interphalangeal (PIP) joint of at least 20 degrees; AND
- **C)** The 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 patients meets ALL of the following criteria (A, B, C, and D):
- **A)** The patient is ≥18 years of age; AND
- **B)** The 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)** The patient has not previously been treated with a complete course (8 injections) of Xiaflex for Peyronie's disease; AND
- **D)** The medication is being administered by a healthcare provider experienced in the treatment of male urological diseases.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Xiaflex 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.)

247. 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.

248. 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.

249. 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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PRIOR AUTHORIZATION POLICY

POLICY: Xyrem Prior Authorization Policy

- Xyrem® (sodium oxybate oral solution – Jazz Pharmaceuticals)

REVIEW DATE: 03/25/2020; selected revision 06/24/2020

OVERVIEW

Xyrem, a central nervous system (CNS) depressant, is indicated for the following uses:[1]

- **Cataplexy treatment in patients with narcolepsy**, in patients ≥ 7 years of age.
- **Excessive daytime sleepiness in narcolepsy**, in patients ≥ 7 years of age.

Guidelines

Guidelines recommend the use of Xyrem for the treatment of narcolepsy and for cataplexy due to narcolepsy.[2-3] 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.

Safety

Xyrem is the sodium salt of gamma hydroxybutyrate (GHB) and is a Schedule III controlled substance.[1] 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 is available only through a restricted distribution program called the Xyrem Success Program, using a centralized pharmacy. Healthcare professionals who prescribe Xyrem and patients must enroll in the Xyrem Success Program and must comply with the requirements to ensure the drug's safe use.

In 2012, the FDA issued a safety communication for Xyrem, reminding healthcare professionals and patients that the combined use of Xyrem with alcohol or CNS depressant drugs can markedly impair consciousness and may lead to severe respiratory depression.[4] At that time, the use of alcohol with Xyrem was a new contraindication added to the Xyrem label, which already contraindicated its use with insomnia medications. The use of Xyrem with other CNS depressant drugs (such as opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, general anesthetics, and muscle relaxants) should generally be avoided.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Xyrem. Because Xyrem has been associated with significant risks, including CNS and respiratory depression, and has the potential for abuse, misuse, and overdose, approval requires Xyrem to be prescribed by a physician who specializes in the condition being treated. 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 is recommended in those who meet the following criteria:

FDA-Approved Indications

35. Cataplexy Treatment in Patients with Narcolepsy. Approve for 1 year if the patient meets the following criteria (A, B, and C):

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) Narcolepsy has been confirmed with polysomnography and a multiple sleep latency test (MSLT); AND

I) Xyrem has been prescribed by a sleep specialist physician or a neurologist.

36. Excessive Daytime Sleepiness in Patients with Narcolepsy. Approve for 1 year if the patient meets the following criteria (A, B, and C):

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) Narcolepsy has been confirmed with polysomnography and a multiple sleep latency test (MSLT); AND

C) Xyrem has been prescribed by a sleep specialist physician or a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Xyrem is not recommended in the following situations:

161. Fibromyalgia. The effectiveness of Xyrem in fibromyalgia has been evaluated in clinical trials of varying size.[5-10] 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.[11-13] Other recommended treatments include TCAs (i.e., amitriptyline), cyclobenzaprine, gabapentin, and SSRIs (i.e., fluoxetine, sertraline, paroxetine).[14]

The European League Against Rheumatism (EULAR) has issued updated evidence-based recommendations for the management of fibromyalgia (2016) stating that initial management should involve patient education and focus on nonpharmacological therapies.[15] 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.

162. 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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PRIOR AUTHORIZATION POLICY

POLICY: Zontivity™ (vorapaxar tablets – Aralez Pharmaceuticals)

APPROVAL DATE: 10/9/2019

OVERVIEW

Zontivity, a protease-activated receptor-1 (PAR-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. The recommended dose is one tablet (Zontivity 2.08 mg) once daily (QD), with or without food. One Zontivity tablet (2.08 mg) is equivalent to 2.5 mg of vorapaxar sulfate. 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.

Clinical Efficacy

The efficacy of Zontivity is supported by a trial called TRA 2°P-TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events-Thrombolysis In Myocardial Infarction 50).[1,2] This study was a multinational, multicenter, randomized, double-blind, placebo-controlled trial that investigated the efficacy of Zontivity in patients with atherosclerosis that affected the coronary (spontaneous MI $\geq$ 2 weeks but $\leq$ 12 months prior), cerebral (ischemic stroke), or peripheral vascular (documented PAD) systems (n = 26,449). The qualifying types of atherosclerosis were MI (67.25%), ischemic stroke (18.45%), and PAD (14.30%). Most patients with a qualifying MI were receiving aspirin therapy (98.1%) and 78.1% of patients reported using a thienopyridine (e.g., clopidogrel). A substantial proportion of patients with a qualifying event of PAD were receiving aspirin (88%); 36.8% of patients were receiving a thienopyridine. The primary endpoint was the composite of CV death, MI, stroke, and urgent coronary revascularization. The median follow up was 2.5 years.[1-2] After a median of 24 months of treatment, the data and safety monitoring board noted that there was an excess of intracranial hemorrhage (ICH) in patients with a history of stroke in the Zontivity group and recommended discontinuation of the medication in all patients with previous stroke, including patients who experienced a new stroke during the study.[2] The trial was permitted to continue in patients without a history of stroke. The 3-year event rate for the composite endpoint in patients who had a prior MI or PAD, without a history of stroke or TIA (n = 20,170), was 10.1% for patients given Zontivity vs. 11.8% in the placebo group (hazard ratio 0.83; 95% confidence interval [CI]: 0.76, 0.90; P < 0.001), an approximate 17% reduction. Of note, among patients

weighing < 60 kg (n = 1,177/20,170), those assigned to receive Zontivity did not have a favorable outcomes compared with the group given placebo.[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) because of the risk of ICH in this patient population.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Zontivity. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zontivity, as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Zontivity to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 3 years in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zontivity is recommended in patients who meet the following criteria:

FDA-Approved Indication

172. Patients with a Previous Myocardial Infarction (MI) or Peripheral Arterial Disease (PAD). Approve if the patient meets the following criteria (A, B and C):

Z) The patient is receiving Zontivity in combination with aspirin and/or clopidogrel; AND

AA) The patient has been determined to be at high risk for future thrombotic events as determined by the prescribing physician (e.g., patient has experienced multiple MIs, has undergone many urgent coronary revascularization procedures, has had placement of coronary artery stents, or the patient has other concomitant diseases that increase CV risk [e.g., diabetes]); AND

BB) The patient weighs ≥ 60 kg.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Zontivity 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.)

163. Acute Coronary Syndrome (ACS) that Occurred Recently (within < 14 days). TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in acute coronary syndrome), which was a multinational, multicenter, double-blind, placebo-controlled, randomized investigation studied the

effects of Zontivity in patients who had experienced an ACS without ST-segment elevation (n = 12,944).[4] Patients were randomized to receive Zontivity (loading dose of 40 mg and then a daily maintenance dose of 2.5 mg thereafter) or matching placebo. Most patients were also receiving a thienopyridine (87.4%) and aspirin (96.9%). The trial was terminated early after a safety review indicated adding Zontivity to standard therapy increased the risk of major bleeding, including ICH. Also, after a median follow-up of 502 days the primary endpoint (death from CV causes, MI, stroke, current ischemia with rehospitalization, or urgent coronary revascularization) was not significantly reduced with adding Zontivity compared with placebo (Kaplan-Meier 2-year rate 18.5% vs. 19.9% respectively; P = 0.07). TRA 2°P-TIMI 50 enrolled patients who were 2 weeks post a spontaneous MI or ischemic stroke.

164. **Patients 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.

165. **Concurrent Use of Effient® (prasugrel tablets) or Brilinta® (ticagrelor tablets).** There is limited clinical experience involving use of Zontivity with antiplatelet agents other than aspirin and/or clopidogrel (e.g., Effient, Brilinta). In the pivotal trial with Zontivity (TRA 2°P-TIMI 50) only 177 patients (0.7%) received Effient during the trial. Further data are needed to determine if Zontivity has efficacy and can be used safely in combination with other antiplatelet medications. In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion.

166. 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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Prior Authorization Policy

POLICY: Zovirax (Topical)

- Zovirax® (acyclovir 5% cream – Valeant, generics)
- Zovirax (acyclovir 5% ointment – Valeant, generics)

APPROVAL DATE: 06/12/2019

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]

Herpes simplex virus type 1 (HSV-1) is mainly transmitted by oral-to-oral contact and causes infections in and around the mouth (oral herpes).[3,4] HSV-1 can also cause genital herpes, but genital herpes is more commonly caused by HSV-2, which is transmitted via sexual contact.

Herpes labialis (cold sores, fever blisters), a highly contagious infection, is a common condition caused by HSV-1.[3,5] This condition is typically self-limiting; many patients do not require or use treatment.[5,6] However, if pharmacologic therapy is desired, it is important to initiate therapy as soon as possible. Topical antiviral medications can be helpful in the treatment of herpes labialis. Approximately one-third of all infected patients experience relapses. Recurrent episodes of herpes labialis can be painful, long-lasting, and disfiguring.[6]

Genital herpes, a chronic, life-long viral infection, requires prompt treatment.[3,4] Systemic antiviral drugs are used to treat first and recurrent episodes and in some cases, systemic antiviral drugs are used as daily suppressive therapy.[4]

Shingles is a viral infection caused by the varicella-zoster virus, the same virus that causes chickenpox.[7,8] 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 <u>not</u> noted as treatment options for shingles.

Policy Statement

Prior authorization is recommended for prescription benefit coverage of Acyclovir 5% cream (Zovirax, generics) and Acyclovir 5% ointment (Zovirax, generics). Use should be limited to the treatment of medical conditions. All approvals are provided for 1 year. For the ointment, a trial of generic acyclovir 5% ointment is required prior to approval of brand Zovirax 5% ointment.

<u>Automation</u>: None.

RECOMMENDED AUTHORIZATION CRITERIA

III. Coverage of <u>acyclovir 5% cream (Zovirax 5% cream, generics)</u> is recommended in those who meet the following criterion:

FDA-Approved Indication

30. Herpes Labialis (Cold Sores) in Immunocompetent Adults and Adolescents ≥ 12 Years of Age. Approve for 1 year.

IV. Coverage of <u>acyclovir 5% ointment (Zovirax 5% ointment, generics)</u> is recommended in those who meet the following criteria:

FDA-Approved Indications

31. Genital Herpes. Approve for 1 year if the patient meets one of the following criteria (A <u>or</u> B):

a. Generic acyclovir 5% ointment is requested; OR
b. If brand Zovirax 5% ointment is requested, the patient has tried generic acyclovir 5% ointment AND 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 prescribing physician, would result in a significant allergy or serious adverse reaction.

32. Limited Non-Life-Threatening Mucocutaneous Herpes Simplex Virus Infections in Immunocompromised Patients. 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 has tried generic acyclovir 5% ointment AND 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 prescribing physician, would result in a significant allergy or serious adverse reaction.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Acyclovir 5% cream (Zovirax cream, generics) and acyclovir 5% ointment (Zovirax ointment, generics) 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.)

15. Shingles.

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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