Uniform Medical Plan (UMP) coverage limits for drugs covered under UMP's prescription drug benefit

Updates effective June 01, 2024

These coverage limits apply to all UMP Plans that the Public Employees Benefits Board (PEBB) and the School Employees Benefits Board (SEBB) offer.

As a state-sponsored health plan, UMP follows the Washington State Pharmacy and Therapeutics (P&T) Committee's coverage recommendations. The committee consists of Washington health care professionals, including physicians and pharmacists. The UMP Preferred Drug List (PDL) aligns with the committee's coverage recommendations and contains useful information such as a drug's coverage limits. The UMP PDL is the same for both Public Employees Benefits Board (PEBB) and School Employees Benefits Board (SEBB) members.

The Washington State P&T committee does not review all drug classes. For all other prescription drug classes, the Washington State Rx Services P&T Committee makes coverage recommendations for UMP to consider. UMP then determines a drug's coverage, including any coverage limits. These drugs are also included on the UMP PDL.

Some prescription drugs require preauthorization to determine whether they are medically necessary and meet UMP coverage criteria. If you do not receive approval for your preauthorization, UMP will not cover these drugs. **To request a preauthorization, a member, pharmacy, or prescribing provider can call Washington State Rx Services at 1-888-361-1611 (TRS: 711).**

Some drugs may only be covered under UMP medical benefits and have different rules for preauthorization. To request a preauthorization for a drug covered under UMP medical benefits, call UMP Customer Service at:

- PEBB Members: 1-888-849-3681 (TRS: 711)
- SEBB Members: 1-800-628-3481 (TRS: 711)

For more information:

- Refer to your plan's current certificate of coverage by visiting **Forms and publications at hca.wa.gov/ump-coc**
- Call Washington State Rx Services at 1-888-361-1611 (TRS: 711)
- Refer to the **UMP Preferred Drug List by visiting hca.wa.gov/assets/pebb/ump-preferred-drug-list-2024.pdf**

Policy Type: PA/SP Pharmacy Coverage Policy: UMP256

Split Fill Management*

Description

Pacritinib (Vonjo) is a Janus associated kinase 2 (JAK2) inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
pacritinib (Vonjo)	Intermediate- or high-risk myelofibrosis with severe thrombocytopenia (platelet count below 50 x 10^9/L)	100 mg capsules	120 capsules/30 days

Initial Evaluation

I. **Pacritinib (Vonjo)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a hematologist or oncologist; **AND**
   C. A diagnosis of **intermediate- or high-risk myelofibrosis** when the following are met:
      1. Splenomegaly is present and spleen volume is documented; **AND**
      2. Member has severe thrombocytopenia (defined as platelet count below 50 x 10^9/L); **AND**
      3. Documentation of disease-related symptoms (e.g., fatigue, shortness of breath, bruising, bleeding, fever, bone pain)

II. Pacritinib (Vonjo) is considered <u>not medically necessary</u> when criteria above are not met and/or when used for:
   A. Myelofibrosis without severe thrombocytopenia (i.e., platelet count is ≥ 50 x 10^9/L)

III. Pacritinib (Vonjo) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Low risk myelofibrosis
   B. Polycythemia vera
   C. Graft versus host disease
   D. Lymphoproliferative neoplasms
   E. Solid tumors (e.g., prostate, colorectal, lung)

F. Acute myeloid leukemia (AML)
G. Chronic lymphocytic leukemia, small lymphocytic lymphoma
H. COVID-19

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. A diagnosis of intermediate- or high-risk myelofibrosis (has not transformed to AML); **AND**
IV. Member has exhibited improvement in or stability of spleen volume; **AND**
V. Member has exhibited improvement in or stability of disease-related symptoms (e.g., fatigue, shortness of breath, bruising, bleeding, fever, bone pain).

Supporting Evidence

I. Myelofibrosis (MF) is a cancer of the bone marrow. Symptoms are non-specific (e.g., fatigue, shortness of breath, bleeding) and splenomegaly is common. Over time MF may progress to acute myeloid leukemia (AML). There are five risk levels of disease that correlate with prognosis, and treatment is based on risk. When patients are not eligible for allogeneic stem cell transplant, symptom targeted therapy may be used in those with intermediate or higher risk MF. Symptomatic therapies include hydroxyurea and JAK inhibitors: ruxolitinib (Jakafi), fedratinib (Inrebic), pacritinib (Vonjo). JAK inhibitors have only been sufficiently evaluated in patients with at least intermediate-risk MF and have unknown clinical value for lower risk disease. JAK inhibitors do not reverse fibrosis or prolong survival but may reduce spleen size and improve disease-related symptoms. In absence of splenomegaly and symptoms, these medications have unknown application. Given the specialized diagnosis, treatment, and monitoring, prescribing by or in consultation with a specialist is required.
II. Ruxolitinib (Jakafi) and fedratinib (Inrebic) are approved for MF in those with a platelet count ≥ 50 x 10^9/L. These medications are known to cause thrombocytopenia and are recommended to be discontinued if the platelet count drops below 50 x 10^9/L. Pacritinib (Vonjo), has a unique approval, and was approved under the accelerated approval pathway based on spleen volume reduction (SVR) when platelet count is under 50 x 10^9/L (severe thrombocytopenia). Pacritinib (Vonjo) has been evaluated in adults; use in pediatrics or adolescents has unknown value or consequences. Outside of a clinical trial setting, therapy should only be utilized in adults.
III. Pacritinib (Vonjo) was evaluated in two Phase 3 trials, PERSIST1 and PERSIST2. The accelerated approval was based on results from PERSIST2, a randomized, open-label trial vs. best available therapy (BAT) (included 39% of patients on ruxolitinib [Jakafi]) for 24 weeks (n=311). Patients had platelets < 100 x 10^9/L (45% had < 50 x 10^9/L). Regimens of 400 mg once daily and 200 mg twice daily were evaluated. Outcomes included spleen volume reduction (SVR) of ≥ 35%, and daily symptom score reduction of at least 50% via the MPN-SAF TSS tool. The trial indicated a

statistically significant improvement in SVR for both treatment arms compared to BAT, and the 200 mg twice daily arm showed an improvement in daily symptoms scores over BAT. Subgroup analyses for the specific FDA-approved population (i.e., platelet count <50 x 10^9/L) were not statistically evaluated. PERSIST1 was a randomized, open-label trial evaluating 400 mg once daily vs. BAT for 24 weeks (n=327). For pacritinib (Vonjo), 148 patients (67%) had platelets > 100 x 10^9/L, 37 (17%) had < 100x10^9/L, and 35 (16%) had < 50 x10^9/L. There was statistical significance over BAT for SVR ≥ 35%, and reduction in TSS ≥ 50%.

IV. There is positive evidence to indicate clinical value of pacritinib (Vonjo) in patients with MF with severe thrombocytopenia; however, given lack of clinical trials focused solely on this specific population, as well as other trials with various doses and conflicting results, the FDA has granted accelerated approval based on SVR, and continued approval is contingent upon verification of clinical benefit in the PACIFICA3 Phase 3 clinical trial. Results are due in 2025. Of note, this therapy is only FDA approved given the already seen impact on SVR and a condition of the accelerated approval, is that the manufacturer confirms that SVR and this therapy leads to a clinical benefit. Until confidence in the clinical benefit is determined, therapy is reserved for those that have reduction in spleen volume and also experience symptom improvement.

V. Given the limited approval of pacritinib (Vonjo), coverage consideration is limited to MF with severe thrombocytopenia and disease-related symptoms. There is unknown clinical value in those without symptoms. Coverage consideration is also limited to those with severe thrombocytopenia as other treatment options with full FDA-approval, stronger evidence for efficacy, and more developed safety profiles are available; ruxolitinib (Jakafi) and fedratinib (Inrebic). Pacritinib (Vonjo) has some evidence for efficacy in patients that have platelet counts above 50 x 10^9/L and could be considered as a treatment option for patients with trial and failure or contraindication to ruxolitinib (Jakafi) and fedratinib (Inrebic); however, when possible, therapy should be reserved for the FDA-approved population as the efficacy and safety profile of pacritinib (Vonjo) continues to develop. In 2016 the FDA put a hold on the trials due to noted deaths from hemorrhage, cardiac failure and arrest. The hold was later lifted in 2017 after evaluation of all clinical trial evidence; however, the safety profile of pacritinib (Vonjo) is not fully understood. One unique black box warning for fedratinib (Inrebic) is encephalopathy, and in those that experience signs/symptoms or are at an increased risk may not be appropriate for fedratinib (Inrebic) use. This has not yet been noted for pacritinib (Vonjo) or ruxolitinib (Jakafi); however, comparative safety and efficacy data for these therapies are not available.

VI. Pacritinib (Vonjo) outcomes of SVR and improvement in daily symptoms were evaluated by week 24; a six-month initial approval is granted to allow sufficient time for and evaluation of symptom response. There is lack of strong evidence to indicate treatment response will occur if not reached by this time. Pacritinib (Vonjo) has shown clinical value in reducing spleen size and improving disease-related symptoms; thus, continuation of therapy is reasonable when both of these are stable or have improved. Reduction in spleen size without improvement in disease-related symptoms has unknown clinical value at this time. Of note, spleen volume or size may be assessed or examined by physical examination (i.e., palpation); however, if the spleen is not palpable, imaging is appropriate for determining spleen size or volume. This is done when there is a need to determine the spleen size or changes when physical examination is insufficient (e.g., for determining response to therapy).

Investigational or Not Medically Necessary Uses

I. Pacritinib (Vonjo) is considered not medically necessary in patients with MF with platelet counts greater than 50 x 10^9/L when patients are eligible for the two JAK inhibitors that are FDA-approved in that population; ruxolitinib (Jakafi) and fedratinib (Inrebic). Ruxolitinib (Jakafi) and fedratinib (Inrebic) have established safety and efficacy profiles for patients with platelets greater than 50 x 10^9/L. In the event of treatment failure or contraindication to these two JAK inhibitors, pacritinib (Vonjo) could be considered a fair treatment option; however, when patients do not have failure or contraindication to ruxolitinib (Jakafi) and fedratinib (Inrebic), use of pacritinib (Vonjo) should be reserved for patients with severe thrombocytopenia.

II. Pacritinib (Vonjo) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Low risk myelofibrosis
   B. Polycythemia vera
   C. Graft vs. host disease
   D. Lymphoproliferative neoplasms
   E. Solid tumors (e.g., prostate, colorectal, lung)
   F. Acute myeloid leukemia (AML)
   G. Chronic lymphocytic leukemia, small lymphocytic lymphoma
   H. COVID-19

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Mesa RA, Vannucchi AM, Mead A, et al. Pacritinib versus best available therapy for the treatment of myelofibrosis irrespective of baseline cytopenias (PERSIST-1): an international, randomised, phase 3 trial. *Lancet Haematol*. 2017;4(5):e225-e236.
2. Mascarenhas J, Hoffman R, Talpaz M, et at. Pacritinib vs best available therapy, including ruxolitinib, in patients with myelofibrosis. A randomized clinical trial. *JAMA Oncol*. 2018;4(5):652-659.
3. Vonjo [Prescribing Information]. CTI Biopharma Corp. Seattle, WA. February 2022.
4. National Comprehensive Cancer Network. NCCN Guidelines: Myeloproliferative Neoplasms. V1.2022, updated 02/28/2022.
5. Jakafi [Prescribing Information]. Incyte Corporation. Wilmington, DE. September 2021.
6. Inrebic [Prescribing Information]. Celgene Corporation. Summit, NJ. August 2019.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
ruxolitinib (Jakafi, Opzelura) Policy	Intermediate or high-risk myelofibrosis
fedratinib (Inrebic) Policy	Myelofibrosis

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2022

Policy Type: PA/SP Pharmacy Coverage Policy: UMP051

Description

Palivizumab (Synagis) is a humanized monoclonal antibody directed against the fusion protein of respiratory syncytial virus (RSV).

Length of Authorization

- Initial: Five months
- Renewal: N/A

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
palivizumab (Synagis)	100 mg/1mL	Respiratory syncytial virus (RSV) prophylaxis	15 mg/kg (1 dose) per 28 days
	50 mg/0.5mL		

Initial Evaluation

I. Palivizumab (Synagis) may be considered medically necessary when the following criteria below are met:
   A. Therapy is given during the current RSV season, **AND**
   B. Member is being managed by, or in consultation with, a pulmonologist or cardiologist; **AND**
   C. A diagnosis of one of the following:
      1. **Preterm Infants WITHOUT congenital morbidities** (e.g. chronic lung disease of prematurity; or congenital heart disease); **AND**
         i. Member was born before 29 weeks, 0 days of gestation; **AND**
         ii. Member is less than 12 months of postnatal age; **OR**
      2. **Preterm Infants WITH Chronic Lung Disease (CLD)**; **AND**
         i. Member was born before 32 weeks, 0 days of gestation; **AND**
         ii. Member required respiratory support (supplement with greater than 21% oxygen) for at least the first 28 days after birth; **AND**
         iii. Member is less than 12 months of age; **OR**
         iv. Member is less than 24 months of age; **AND**
         v. Continues to require medical support (e.g., chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the 6-month period before the start of second RSV season; **OR**
      3. **Infants and Children with Hemodynamically Significant Congential Heart Disease (CHD)**; **AND**
         i. Member is less than 12 months of age; **AND**
         ii. Member has moderate to severe pulmonary hypertension; **OR**
         iii. Member has cyanotic heart disease; **OR**

iv. Member has acyanotic heart disease; **AND**
    a. Member is receiving medication to control congestive heart failure; **AND**
    b. Member will require cardiac surgical procedures; **OR**

4. **Children undergoing cardiac transplantation during RSV season**; **AND**
    i. Member is less than 24 months of age; **OR**
5. **Infants with Anatomic Pulmonary Abnormalities or Neuromuscular disorder**; **AND**
    i. Member is less than 12 months of age; **AND**
    ii. Member has an impaired ability to clear secretions from the upper airway; **OR**
6. **Immunocompromised Children**; **AND**
    i. Member is less than 24 months of age; **AND**
    ii. Member is profoundly immunocompromised (e.g. undergoing chemotherapy, HIV, SCID, DiGeorge, IgA deficiency, Hypergammaglobulinemia etc.); **OR**
7. **Children with Cystic Fibrosis, Primary Ciliary Dyskinesia, or other rare lung disease**; **AND**
    i. Member is less than 12 months of age; **AND**
        a. Member has clinical evidence of chronic lung disease (CLD); **OR**
        b. Member has clinical evidence of nutritional compromise; **OR**
    ii. Member is less than 24 months of age; **AND**
        a. Member had a hospitalization for pulmonary exacerbation in the first year of life; **OR**
        b. Member has abnormalities on chest radiography/chest computed tomography that persist when stable; **OR**
        c. Member has a weight for length less than the 10th percentile

II. Palivizumab (Synagis) is considered <u>not medically necessary</u> when criteria above are not met and/or when used for:
    A. Infants or children who were born after 32 weeks
    B. Infants and children with hemodynamically insignificant heart disease such as:
        1. Secundum atrial septal defect
        2. Small ventricular septal defect
        3. Pulmonic stenosis
        4. Uncomplicated aortic stenosis
        5. Mild coarctation of the aorta
        6. Patent ductus arteriosus
    C. Infants with lesions adequately corrected by surgery, unless they continue to require medication for congestive heart failure
    D. Infants with mild cardiomyopathy who are not receiving medical therapy for the condition
    E. Children in the second year (≥24 months) of life
    F. Children with Down syndrome without other comorbid conditions listed in the Initial Evaluation (section I) portion of this policy.

III. Palivizumab (Synagis) is considered investigational when used for all other conditions, including but not limited to:
   A. For the treatment of RSV

Supporting Evidence

I. For current RSV trends, refer to: http://www.cdc.gov/surveillance/nrevss/rsv/index.html. The CDC utilizes the past year's surveillance season data to predict the timing of the next year's outbreak.

II. Palivizumab (Synagis) is a respiratory syncytial virus (RSV) F protein inhibitor monoclonal antibody indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients. The FDA approved palivizumab (Synagis) in 1998 for pediatric patients with a history of premature birth (<35 weeks of gestation), children with bonchopulmonary dysplasis (BPD), and those with hemodyanamically significant congenital heart disease (CHD).

III. The American Academy of Pediatrics (AAP) committee on infectious diseases (COID) has undertaken a systematic review of all recent, and older, peer-reviewed literature relating to the burden of respiratory syncytial virus (RSV) disease in infants and children, specifically focusing on publications that delineate children at greatest risk of serious RSV disease and studies that define pharmacokinetics, safety, and efficacy. Detailed input regarding this guidance has been solicited from 21 committees, councils, sections, and advisory groups within the AAP, as well as organizations outside the AAP. The updated (reviewed every 3 years) recommendations by AAP are based on review of the quality of all available data, as well as real world clinical impact of palivizumab (Synagis) prophylaxis for the population subset in the United States.

IV. Available clinical data and the AAP recommendations note that there is limited clinical benefit derived from palivizumab prophylaxis for otherwise healthy infants and children and therefore, should be limited to the patient population described in this policy. Furthermore, the package insert for palivizumab (Synagis) states: "Synagis is indicated for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease." And in the absence of a specific definition of "high risk" by the US FDA, the AAP has provided guidenace for determinining the "high risk" population characetistics which have been used to create this policy.

V. Palivizumab (Synagis) was evaluated in two randomized, double-blind, placebo-controlled trials of prophylaxis against RSV infection in children at high risk of an RSV-related hospitalization.
   - Trial 1 was conducted during a single RSV season with 1502 children who were less than or equal to 24 months of age with bronchopulmonary dysplasia (BPD) or infants with premature birth (less than or equal to 36 weeks of gestation) who were less than or equal to 6 months of age at study entry.
     i. Results of Trial 1: 4.8% (49/1002) participants were hospitalized in the palivizumab (Synagis) group compared to 10.6% (52/500) participants were hospitalized in the placebo group.

- Trial 2 was conducted over four consecutive RSV seasons with 1287 children less than or equal to 24 months of age with hemodynamically significant congenital heart disease.
    i. Results of Trial 2: 5.3% (34/639) participants were hospitalized in the palivizumab (Synagis) group compared to 9.7% (63/648) participants were hospitalized in the placebo group.

VI. A technical review by the American Academy of Pediatrics (AAP) was completed in 2014 and the recommendation was palivizumab (Synagis) for RSV prophylaxis "cannot be considered as high-value health care for any group of infants" because there is minimal benefit, in addition to its high cost. From that technical review, AAP published the following guidance in 2014: Palivizumab (Synagis) Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection.
- The AAP states available data for infants born at 29 weeks, 0 days' gestation or later do not identify a clear gestational age cutoff for which the benefits of prophylaxis are clear. For this reason, infants born at 29 weeks, 0 days' gestation or later are not universally recommended to receive palivizumab (Synagis) prophylaxis. Infants 29 weeks, 0 days' gestation or later may qualify to receive prophylaxis on the basis of congenital heart disease (CHD), chronic lung disease (CLD), or another condition.

VII. For preterm infants born before 32 weeks, 0 days of gestational age, palivizumab (Synagis) prophylaxis is recommended if the infant developed chronic lung disease (CLD) of prematurity. This typically involves use of supplemental Oxygen (O_2) therapy during the first 28 days after birth to mitigate hypoxia and cyanosis. While normal O_2 saturation in inspired room air (FiO_2) is 20%, infants with CLD require supplementation with > 21% O_2 concentration. The Oxygen need is determined by the patient's disease severity and can range from 21% to up to 100%. Per WHO recommendations for treatment of CLD, supplemental Oxygen therapy should be initiated with 30% oxygen or air (if blended oxygen is not available), rather than with 100% oxygen. The use of progressively higher concentrations of oxygen should only be considered for newborns undergoing oxygen therapy if their heart rate is less than 60 beats per minute after 30 seconds of adequate ventilation with 30% oxygen or air.

VIII. AAP guidelines recommend palivizumab (Synagis) for infants with hemodynamically significant CHD. In this setting, the best therapeutic benefit is likely for infants with acyanotic heart disease who are receiving medication to control congestive heart failure and will require cardiac surgical procedures and in infants with moderate to severe pulmonary hypertension. Decisions regarding palivizumab prophylaxis for infants with cyanotic heart defects in the first year of life may be made in consultation with a pediatric cardiologist. According to recommendations from key experts in pediatric cardiology, infants with cyanotic heart defects (e.g. heart valve defects, Ebstein anomaly, hypoplastic left heart syndrome, Tetralogy of Fallot, Truncus arteriosus) are at a much higher risk of complications from RSV as compared to those with acyanotic heart defects (e.g. congential septal defects, patent ductus arteriosus, pulmonary stenosis, aortic stenosis). Consequently, prophylaxis using palivizumab (Synagis) may have a significant, real world clinical and potentially life-saving impact for the infant population with cyanotic heart disease. AAP guidelines recommend that the decision to use palivizumab (Synagis) in cyanotic heart disease patients must be made by or in consultation with a pediatric cardiologist.

IX. During the second year of life, consideration of palivizumab prophylaxis is recommended only for infants who satisfy the definition of CLD of prematurity and continue to require medical support (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the 6-

month period before the start of the second RSV season. For infants with CLD who do not continue to require medical support in the second year of life prophylaxis is not recommended.

X. Although the National Perinatal Association 2018 Respiratory Syncytial Virus (RSV) Prevention Clinical Practice Guideline: An Evidence-Based Interdisciplinary Collaboration published additional guidance and new information as it relates to RSV, after reviewing the new information, the AAP still recommended their guidelines from 2014 as the new evidence did not change the cost-benefit analysis that was done.

Investigational or Not Medically Necessary Uses

I. The listed diagnoses are included in the AAP 2017 RSV Guidance as not medically necessary for immunoprophylaxis with palivizumab (Synagis)
   - A. Infants or children who were born after 32 weeks
   - B. Infants and children with hemodynamically insignificant heart disease such as:
     - i. Secundum atrial septal defect
     - ii. Small ventricular septal defect
     - iii. Pulmonic stenosis
     - iv. Uncomplicated aortic stenosis
     - v. Mild coarctation of the aorta
     - vi. Patent ductus arteriosus
   - C. Infants with lesions adequately corrected by surgery, unless they continue to require medication for congestive heart failure
   - D. Infants with mild cardiomyopathy who are not receiving medical therapy for the condition
   - E. Children in the second year (≥24 months) of life
   - F. Children with Down syndrome without other comorbid conditions listed in the Initial Evaluation (section I) portion of this policy.

II. Treatment of RSV
   - A. Safety and efficacy has not been established for the use of palicizumab (Synagis) for the treatment of RSV.

References

1. Synagis [Prescribing Information]. Gaithersburg, MD: MedImmune, LLC. March 2014.Wegzyn C, Toh LK, Biguenet S, et al. Safety and Effectiveness of Palivizumab in Children at High Risk of Serious Disease Due to Respiratory Syncytial Virus Infection: A Systematic Review. Infect Dis Ther. 2014 Dec; 3(2): 133–158.
2. American Academy of Pediatrics: Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection. Available at: https://pediatrics.aappublications.org/content/134/2/415
3. American Academy of Pediatrics: RSV recommendations unchanged after review of new data. Available at: https://www.aappublications.org/news/2017/10/19/RSV101917
4. Policy Statement: Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. American Academy of Pediatrics Committee on Infectious Diseases; American Academy of Pediatrics Bronchiolitis Guidelines Committee. *Pediatrics.* August 2014; 134(2): e415-20. doi: 10.1542/peds.2014-1665. Reaffirmed February 2019. Available online at https://pediatrics.aappublications.org/content/134/2/415.full#sec-13.

5. Goldstein M, Phillips R, DeVincenzo J, et al. The National Perinatal Association 2018 Respiratory Syncytial Virus (RSV) Prevention Clinical Practice Guideline: An Evidence-Based Interdisciplinary Collaboration. October 2017.
6. Center for Disease Control and Prevention: Respiratory Syncytial Virus Infection (RSV). Available at: https://www.cdc.gov/rsv/clinical/index.html
7. Red Book® 2018. Committee on Infectious Diseases; American Academy of Pediatrics; David W. Kimberlin, MD, FAAP; Michael T. Brady, MD, FAAP; Mary Anne Jackson, MD, FAAP; Sarah S. Long, MD, FAAP. Section 3: Respiratory Syncytial Virus. Available at https://redbook.solutions.aap.org/Book.aspx?bookid=2205. Accessed December 4th, 2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Formatting edits and minor edits to wording used in efforts to provide more clarity of policy intent; Addition of indication of 'cyanotic heart disease' as per AAP guidelines; Updated Supporting Evidence section to include more information surrounding clinical benefits of palivizumab (Synagis) prophylaxis and clarification that this policy follows AAP recommendations based on quality of clinical evidence instead of FDA approved indications listed in package insert	12/2020
Transitioned criteria into policy with supporting evidence, and incorporated the updated AAP RSV prophylaxis guidelines that details the specific coverage recommendations for: chronic lung disease in patients less than 24 months, patients less than 12 months with hemodynamically significant chronic heart disease, cardiac transplantation in patients less than 24 months, anatomic pulmonary abnormalities/neuromuscular disorder in patients less than 12 months, immunocompromised children, children with rare lung disease. Additionally, incorporated the recommendations from the updated AAP RSV prophylaxis guidelines to detail what diagnoses are not medically necessary for RSV prophylaxis/Synagis.	09/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP297

Description

Palovarotene (Sohonos) is a selective retinoic-acid receptor gamma (RARγ) agonist.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form*	Quantity Limit
palovarotene (Sohonos)	Fibrodysplasia ossificans progressiva (FOP)	1 mg capsule	30 capsules/30 days
		1.5 mg capsule	
		2.5 mg capsule	
		5 mg capsule	
		10 mg capsule	

**See appendix for weight-based dosing for pediatric patients*

Initial Evaluation

I. **Palovarotene (Sohonos)** may be considered medically necessary when the following criteria are met:
   A. Member is 8 years of age or older and female; **OR**
      1. Member is 10 years of age or older and male; **AND**
   B. Documentation of weight within the last three months if under the age of 18 years; **AND**
   C. Medication is prescribed by, or in consultation with, a specialist from the FOP centers of excellence [found here: Research Centers - IFOPA - International Fibrodysplasia Ossificans Progressiva Association]; **AND**
   D. A diagnosis of **fibrodysplasia ossificans progressiva (FOP)** when the following are met:
      1. Documentation of the *ACVR1* mutation; **AND**
      2. Provider attestation that the member has the following clinical features:
         i. Member has bilateral malformation of the big toes [characteristically short and laterally deviated (hallux valgus) and absent or fused joint]; **AND**
         ii. Member has presence of soft tissue ossification

II. Palovarotene (Sohonos) is considered investigational when used for all other conditions, including but not limited to:
   A. Juvenile fibromatosis/desmoid tumors
   B. Progressive osseous heteroplasia (POH)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Provider attestation that palovarotene (Sohonos) continues to slow or stabilize the progression of disease and treatment provides clinical benefit to the member.

Supporting Evidence

I. Palovarotene (Sohonos) was approved for the reduction in the volume of new heterotrophic ossification (HO) in adults and children aged eight and older for females and ten and older for males with a diagnosis of fibrodysplasia ossificans progressiva (FOP).
II. Due to the rarity and complexity of FOP, diagnosis and treatment should be done by, or in consultation with, a physician who specializes in rare connective tissue diseases. Currently there are four centers that specialize in FOP in the continental United States, and it is recommended that the patients primary care physician consult with one in the path to treatment.
III. FOP is an ultra-rare, genetic connective tissue disorder characterized by severe, progressive development of bone in areas outside of the skeleton (heterotopic ossification; HO), such as the ligaments, tendons, and muscles. The hallmark symptom of FOP is malformation of the big toes at birth; the big toe presents as short, bent, and usually curved inward with a missing joint. Episodes of painful soft tissue swelling, known as flare-ups, begin during the first decade of life, and these are often precipitated by soft tissue injury, intramuscular injections, viral infections, or falls. These flare-ups may lead to extra skeletal HO, which progresses throughout life. Over time, HO eventually leads to stiffness in affected areas, limited movement, and eventual ankylosis (fusion) of affected joints. Many individuals with FOP are confined to a wheelchair by their 30s, requiring lifelong assistance with activities of daily living. The estimated median lifespan of individuals with FOP is 56 years; death is often due to cardiorespiratory failure as a result of severe restriction of the chest wall.
IV. FOP is caused by mutations in the activin A receptor type 1 gene (*ACVR1*), which encodes a bone morphogenetic protein (BMP) type I receptor that is important during the formation of the skeleton in the embryo and the repair of the skeleton following birth. The mutation in the *ACVR1* gene increases BMP signaling, resulting in the formation of heterotopic bone. Approximately 97% of patients with FOP have the same *ACVR1* point mutation (arginine to histidine [R206H]), which is considered classic FOP. A diagnosis of FOP may be confirmed by clinical evaluation, characteristic physical findings, and sequencing of the *ACVR1* gene; historically patients were confirmed by physical findings and diagnosis by elimination, the *ACVR1* gene is more routinely tested for in patients in present day. Palovarotene (Sohonos) helps decrease this BMP signaling, allowing normal tissue repair.
V. Whole body computed tomography (WBCT) can be done to assess and track new HO; however, this is not routinely done in practice outside of the four FOP centers or in a clinical trial. The majority of providers assess patient disease progression based on physical exam and provider or patient assessment tools such as the Fibrodysplasia Ossificans Progressiva Physical Function

Questionnaire (FOP-PFQ) or the Cumulative Analogue Joint Involvement Scale (CAJIS). There are several FOP-PFQ depending on age, but those 15 and over are self-reported with 28 items rated 1 to 5 with 5 being able to do the task without help and without use of any assistive device or aid, including a wheelchair. A higher score is more normal functioning, whereas a lower score is worsened disease. CAJIS is a provider scoring of mobility limitations of 15 sites of the body (three axial: neck, jaw, thoraco-lumbar spine), six upper body and six lower body (including each shoulder, wrist, hip, socket, ankle, knee). Each site is assessed for regular movement (score zero), partially impaired (score one), and fully immobile (score two), with a higher score meaning more HO over the body and more immobilization. It is important to note that these tools are newer in development and physicians may use other non-traditional scales or monitoring to track patients, such as ability to fully expand and reach arms out from the body (assessing shoulder and elbow HO).

VI. To date, the 2022 International Clinical Council on FOP lists management as predominantly supportive and focuses on prevention of flare-ups and improving quality of life. These preventive measures include things like preventing falls by installing handrails or wearing headgear, avoiding unnecessary surgeries, and preventing viral illnesses via hand washing and hand sanitizer, as routine immunizations may cause flares. The first line pharmaceutical treatment option is a short course of glucocorticoids taken within 24 hours of trauma and continued over three to four days to decrease HO from flare-up or the use of a nonsteroidal anti-inflammatory drug (NSAID) like ibuprofen; there is no preventive therapy in the guidelines.

VII. Palovarotene (Sohonos) was studied in a single-arm, multicenter, 48-month, Phase 3 clinical trial (MOVE) evaluating the safety and efficacy in those with FOP using an outside control, the National Health Service's (NHS) FOP registry in untreated individuals (n=101); matched as closely as possible to those in the NHS registry by age and gender. Patients (n=99) were four years of age and older, weighing at least 10 kilograms, with a diagnosis of FOP. Patients were allowed in the study without a known *ACVR1* gene mutation, but the primary analysis only included those with the *ACVR1-R206H* gene mutation. All patients received chronic treatment, 5mg once daily, with increased dosing at the time of a flare-up or a substantial high-risk traumatic event likely to lead to a flare-up, 20 mg once daily for four weeks followed by 10 mg once daily for 8 weeks, before returning to maintenance. The primary endpoint was the annualized change in new HO volume versus untreated NHS patients measured by low-dose whole-body computed tomography [WBCT]. At the end of the 48 months, the mean annualized HO in cm^3/year was 9.4 in those treated with palovarotene (Sohonos) and 20.3 in the NHS registry. This was a treatment difference of 10.9 cm^3/yr (95% CI; -21.9, -0.6 p=0.039) or a reduction of 54% in the new volume with palovarotene (Sohonos) versus untreated NHS registry.

VIII. The overall quality of evidence is considered low. Although, palovarotene (Sohonos) showed a statistically significant change in the annualized new HO volume, this is not a validated endpoint in FOP and the clinical significance of this remains unknown. Additionally, the trial did not show differences between the number of flares the patients in the trial experienced, the number of new HO sites, or quality of life measures in the patients of the study. The true significance of palovarotene (Sohonos) will be learnt in real-world application. Additionally, the International Clinical Council put out a statement in August 2023 acknowledging palovarotene (Sohonos) as the first next steps in disease treatment, but noted caution with use due to the serious adverse effects of the drug and the unknown clinical meaning of the decrease in new HO.

IX. All patients in the trial experienced at least one adverse event (AE). The most commonly reported were mucocutaneous events such as dry skin (68.7%), lip dryness (46.5%), alopecia (34.3%), pruritus (26.3%), and musculoskeletal events such as arthralgia (33.3%). There was also a large number of dose reductions, mainly related to mucocutaneous ADE. The incidence of dose reduction was higher during flare-up treatment (34.3%) than during chronic treatment (5.1%), as was the overall incidence of dose reduction due to other TEAEs (flare-up treatment: 40.0%; chronic treatment: 11.1%). Adverse reactions leading to permanent discontinuation occurred in 11 (8%) palovarotene treated subjects with dry skin being the most common cause in 2 (1%) subjects. The label also includes a warning for embryo-fetal toxicity and premature epiphyseal closure in growing pediatric patients. The latter occurred in 21 (15%) of the 8 to 10 year or older palovarotene (Sohonos) population.

Investigational or Not Medically Necessary Uses

I. Palovarotene (Sohonos) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Juvenile fibromatosis/desmoid tumors
   B. Progressive osseous heteroplasia (POH)

Appendix

I. Once daily dosing recommendation for pediatric patients aged 8 to 13 years for females and 10 to 13 for males:

Weight	Daily Dosage	Week 1 to 4 Flare-up Dosage	Week 5 to 12 Flare-up Dosage
10 kg to 19.9 kg	2.5 mg	10 mg	5 mg
20 kg to 39.9 kg	3 mg	12.5 mg	6 mg
40 kg to 59.9 kg	4 mg	15 mg	7.5 mg
≥ 60 kg	5 mg	20 mg	10 mg

References

1. Sohonos. Package Insert. Ipsen Biopharmaceuticals, Inc. Cambridge, MA. August 2023.
2. International Clinical Council on FOP (ICC) and Consultants. The Medical Management of Fibrodysplasia Ossificans Progressiva: Current Treatment Considerations. 2022. Accessed October 10, 2022. ICC_guidelines-updated-May-2022.pdf
3. Pignolo RJ, Hsiao EC, Al Mukaddam M, et al. Reduction of New Heterotopic Ossification (HO) in the Open-Label, Phase 3 MOVE Trial of Palovarotene for Fibrodysplasia Ossificans Progressiva (FOP). *J Bone Miner Res*. 2023;38(3):381-394. doi:10.1002/jbmr.4762

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2024

Policy Type: PA/SP Pharmacy Coverage Policy: UMP196

Description

Panobinostat (Farydak) is an orally administered histone deacetylase inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: Six months (can only be renewed once)

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
panobinostat (Farydak)	10 mg capsules	Multiple Myeloma with ≥2 prior regimens, including bortezomib and an immunomodulatory agent	6 capsules/21 days
	15 mg capsules		
	20 mg capsules		

Initial Evaluation

I. Panobinostat (Farydak) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a hematologist or oncologist; **AND**
   C. Not used in combination with any other oncology therapy unless outlined below; **AND**
   D. A diagnosis of **multiple myeloma** when the following are met:
      1. Provider attests member has received at least two prior regimens including both of the following:
         i. Bortezomib (Velcade); **AND**
         ii. Immunomodulatory agent (e.g., thalidomide, lenalidomide, pomalidomide); **AND**
      2. Provider attests panobinostat (Farydak) will be used in combination with one of the following:
         i. Bortezomib (Velcade) AND dexamethasone *only*; **OR**
         ii. Lenalidomide (Revlimid) AND dexamethasone *only*; **OR**
         iii. Carfilzomib (Kyprolis) *only*

II. Panobinostat (Farydak) is considered investigational when used for all other conditions, including but not limited to:
   A. Multiple myeloma when given as part of a quadruplet ("quad") regimen

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Medication is prescribed by, or in consultation with, an oncologist; **AND**
III. Member is responsive to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
IV. Member will not receive more than a total treatment duration of 48 weeks; **AND**
V. Provider attests panobinostat (Farydak) will be used in combination with one of the following:
   A. Bortezomib (Velcade) AND dexamethasone *only*; **OR**
   B. Lenalidomide (Revlimid) AND dexamethasone *only*; **OR**
   C. Carfilzomib (Kyprolis) *only*

Supporting Evidence

I. Panobinostat (Farydak) is FDA-approved for use in combination with bortezomib and dexamethasone and is indicated in the treatment of patients with multiple myeloma who have received at least two prior regimens, including bortezomib and an immunomodulatory agent. 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.
II. The recommended starting dose of panobinostat (Farydak) is 20 mg, taken orally once every other day for three doses per week (on Days 1, 3, 5, 8, 10, and 12) of Weeks 1 and 2 of each 21-day cycle for eight cycles. Treatment continuation may be considered for an additional eight cycles (total 16 cycles) for patients with clinical benefit, unless they have unresolved severe or medically significant toxicity. The total duration of treatment may be up to 16 cycles (48 weeks).
III. Panobinostat (Farydak) was studied in 768 subjects from one Phase 3, double-blind, placebo-controlled, multicentered, multi-country trial. The trial included subjects with one to three previous treatments. Subjects were randomized 1:1 to receive panobinostat (Farydak) + bortezomib and dexamethasone (PAN-BTZ-Dex) or placebo + bortezomib and dexamethasone (PBO-BTZ-Dex) stratified by prior use of bortezomib and the number of prior lines of anti-myeloma therapy. The primary endpoint was progression free survival (PFS), and a key secondary endpoint was overall survival (OS).
   - Median PFS was 11.99 months (95% CI 10.33-12.94) PAN-BTZ-Dex compared to 8.08 months (95% CI 7.56-9.23) PBO-BTZ-Dex, with HR 0.63 (95% CI 0.52-0.76) p<0.0001.

	Median Progression-Free Survival (95% CI, mo [n])		Hazard Ratio (95% CI)
	PAN-BTZ-Dex	Placebo-BTZ-Dex	
Prior use of immunomodulatory drugs (n=485)	13.14 (11.56-15.47)	10.41 (7.95-11.53)	0.54 (0.43-0.68)
Prior use of immunomodulatory drugs and bortezomib (n=193)	11.99 (9.69-13.90)	8.31 (6.14-12.32)	0.52 (0.36-0.76)
Previous use of immunomodulatory drugs, bortezomib, and two or more lines (n=147)	11.99 (9.69-13.37)	6.97 (4.86-13.40)	0.47 (0.31-0.72)

- Matured median OS was 40.3 months (95% CI 35-44.8) PAN-BTZ-Dex compared to 35.8 months (95% CI 29-40.6) PBO-BTZ-Dex, with HR 0.94 (95% CI 0.78–1.14) p=0.54.

	Median Overall Survival (95% CI, mo [n])		Hazard Ratio (95% CI)
	PAN-BTZ-Dex	Placebo-BTZ-Dex	
Prior use of immunomodulatory drugs (n=485)	36.2 (31.18–41.36)	29.4 (24.57–37.78)	0.94 (0.74–1.19)
Prior use of immunomodulatory drugs and bortezomib (n=193)	27.2 (24.21–34.63)	24.7 (17.48–35.38)	1.03 (0.72–1.47)
Previous use of immunomodulatory drugs, bortezomib, and two or more lines (n=147)	25.5 (19.58–34.33)	25.5 (19.58–34.33)	1.01 (0.68–1.50)

IV. Although the clinical trial evaluated subjects with one to three previous treatments, as stated in the package insert, the approval of panobinostat (Farydak) was based upon the efficacy and safety in a prespecified subgroup analysis of 193 patients who had received prior treatment with both bortezomib and an immunomodulatory agent and a median of two prior therapies as the benefit to risk profile appeared to be greater in this more heavily pretreated population than in the overall trial population.

V. Panobinostat (Farydak) is associated with significant toxicity. Clinical trial discontinuation rate was 36% in the panobinostat (Farydak) group, due to adverse events, as compared to 20% in the placebo group. Moreover, discontinuation rate due to Grades 3 or 4 adverse events was 25% in the panobinostat (Farydak) group compared to 13% in the placebo group. However, split fill management is not applicable because only a total of six panobinostat (Farydak) capsules are given per 21-day cycle.

VI. Panobinostat (Farydak) is a REMS agent, carrying a black box warning for fatal and serious toxicities of severe diarrhea and cardiac toxicities.
- Common adverse events (≥20%) are diarrhea, fatigue, nausea, peripheral edema, decreased appetite, pyrexia, and vomiting.
- Common non-hematologic abnormalities (≥40%) are hypophosphatemia, hypokalemia, hyponatremia, and increased creatinine.
- Common hematologic abnormalities (≥60%) are thrombocytopenia, lymphopenia, leukopenia, neutropenia, and anemia.

VII. Per NCCN V2.2021 guidelines, panobinostat (Farydak) + bortezomib and dexamethasone is a Category 1 “other recommended regimen” for previously treated multiple myeloma. Other combinations that do not include panobinostat (Farydak) are considered “preferred”. NCCN guidelines recommend that panobinostat (Farydak) + carfilzomib (Category 2A) OR panobinostat + lenalidomide and dexamethasone (Category 2A) may be useful in certain circumstances and state that such treatment is only indicated for patients who have received at least two prior therapies, including bortezomib and an immunomodulatory agent; guidelines do not define circumstances.
- Panobinostat (Farydak) + lenalidomide and dexamethasone was studied in a multicenter phase I/II study. Primary endpoint of phase II was ORR, which was 82%, and the clinical benefit rate was 91%.

- Panobinostat (Farydak) + carfilzomib was studied in a single-center, phase II study in 27 patients. Primary endpoint was ORR, which was 41%. PFS was 7.1 months.

Investigational or Not Medically Necessary Uses

I. Panobinostat (Farydak) has not been sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Quadruple ("quad") regimen
      i. Although triplet regimens remain the standard of care for multiple myeloma, there is growing interest in quad regimens which may include the addition of monoclonal antibodies (e.g., daratumumab [Darzalex], elotuzumab [Empliciti]) to standard triplet backbone regimens. The current evidence available to support this use is limited to case series or small trials. Larger studies evaluating the safety and efficacy of these regimens are underway.

Appendix

I. Table 1: Recommended Dosing Schedule of panobinostat (Farydak) in Combination with Bortezomib and Dexamethasone During Cycles 1 to 8

21-Day Cycle														
Cycles 1 to 8 (3-Week cycles)	**Week 1 Days**							**Week 2 Days**						**Week 3**
FARYDAK	1		3		5			8		10		12		Rest period
Bortezomib	1			4				8			11			Rest period
Dexamethasone	1	2		4	5			8	9		11	12		Rest period

II. Table 2: Recommended Dosing Schedule of panobinostat (Farydak) in Combination with Bortezomib and Dexamethasone During Cycles 9 to 16

21-Day Cycle														
Cycles 9 to 16 (3-Week cycles)	**Week 1 Days**							**Week 2 Days**						**Week 3**
FARYDAK	1		3		5			8		10		12		Rest period
Bortezomib	1							8						Rest period
Dexamethasone	1	2						8	9					Rest period

III. Table 3: Classification of Medications used for Multiple Myeloma

Proteasome Inhibitors	**Immunomodulatory Agents**	**Monoclonal Antibodies**	**Histone Deacetylase Inhibitors**	**B-cell Maturation Antigen-Directed Antibody**	**Chemotherapy**
• bortezomib • carfilzomib • ixazomib	• thalidomide • lenalidomide • pomalidomide	• elotuzumab • daratumumab • isatuximab-irfc	• panobinostat	• belantamab mafodotin-blmf	• cyclophosphamide • doxorubicin • cisplatin • etoposide • melphalan • bendamustine

References

1. Farydak [Prescribing Information]. Las Vegas, NV: Secura Bio, Inc. September 2019.
2. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Multiple Myeloma Version 2.2021. 2020 September 9; National Comprehensive Cancer Network. Available from: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf

Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria transitioned to policy format. Removed requirements around counseling on side effects and attesting to lack of recent myocardial infarction or unstable angina. Addition of supporting evidence and additional combination agent options [addition of lenalidomide (Revlimid) and dexamethasone; or carfilzomib (Kyprolis)].	10/2020
Criteria created	03/2015

Policy Type: PA/SP Pharmacy Coverage Policy: UMP167

Description

Parathyroid hormone (Natpara) is subcutaneously administered, FDA-approved hormone replacement therapy for hypoparathyroidism. Parathyroid hormone acts to regulate the body's calcium levels.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
Parathyroid hormone (Natpara)	25 mcg/dose cartridge	Adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism	2 cartridges/28 days
	50 mcg/dose cartridge		2 cartridges/28 days
	75 mcg/dose cartridge		2 cartridges/28 days
	100 mcg/dose cartridge		2 cartridges/28 days

Initial Evaluation

I. Parathyroid hormone (Natpara) may be considered medically necessary when the following criteria below are met:
   A. Member is being treated for hypocalcemia due to hypoparathyroidism; **AND**
   B. Member does not have following:
      1. Hypoparathyroidism due to calcium-sensing receptor mutations
      2. Acute post-surgical hypoparathyroidism; **AND**
   C. Member does not have a history of Page's disease of bone, open epiphyses, radiation therapy involving the skeleton, or hereditary disorders predisposing to osteosarcoma; **AND**
   D. Member has tried and failed treatment with calcium supplements and active forms of vitamin D (e.g. calcitriol); **AND**
   E. Member will be treated with this medication adjunct to calcium and vitamin D

II. Parathyroid hormone (Natpara) is considered investigational when used for all other conditions, including but not limited to:
   A. Hypoparathyroidism due to calcium-sensing receptor mutation
   B. Acute post-surgical hypoparathyroidism

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through the health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise; **AND**
III. Member has exhibited improvement or stability of disease symptoms

Supporting Evidence

I. Parathyroid hormone (Natpara) is FDA approved as adjunctive therapy with calcium + vitamin D to control hypocalcemia in patients with hypoparathyroidism.
II. Parathyroid hormone (Natpara) acts to regulate the body's calcium levels. Parathyroid hormone increases the rate of bone turnover by stimulating osteoclast and osteoblast activity, which leads to calcium resorption from bone. The net effects of parathyroid hormone are increases in serum calcium and magnesium concentration and decreased phosphate concentration.
III. Parathyroid hormone (Natpara) has not been studied in patients with hypoparathyroidism due to calcium sensing receptor mutation or patients with acute post-surgical hypoparathyroidism.
IV. Parathyroid hormone (Natpara) has a Black Box warning for use in patients with increased risk of osteosarcoma. Due to this potential risk, parathyroid hormone (Natpara) should be used only in patients who cannot be well-controlled on calcium and active forms of vitamin D.

Investigational Uses

I. Parathyroid hormone (Natpara) is not intended for use in members with hypoparathyroidism due to calcium-sensing receptor mutations, or acute post-surgical hypoparathyroidism.

References

1. Natpara [Prescribing Information]. Lexington, MA: Shire-NPS Pharmaceuticals, Inc., 2018.

Policy Implementation/Update:

Date Created	January 2015
Date Effective	January 2015
Last Updated	November 2019
Last Reviewed	11/2019

Action and Summary of Changes	Date
Criteria updated to new policy format.	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP146

Description

Teriparatide, teriparatide (Forteo), and abaloparatide (Tymlos) are human parathyroid hormone related peptide [PTHrP (1-34)] analogs.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
teriparatide (Forteo)	Primary Osteoporosis/Hypogonadal-related Osteoporosis in Men Post-Menopausal Osteoporosis in Women Glucocorticoid-induced Osteoporosis	600 mcg/2.4 mL pen-injector	1 pen (2.4 mL)/28 days
generic teriparatide			
teriparatide (biosimilar formulation)		620 mcg/2.48 mL pen-injector	1 pen (2.48 mL)/28 days
abaloparatide (Tymlos)	Primary Osteoporosis/Hypogonadal-related Osteoporosis in Men Post-Menopausal Osteoporosis in Women	3120 mcg/1.56 mL (2000 mcg/mL)	1 pen (1.56 mL)/30 days

Initial Evaluation

I. **Abaloparatide (Tymlos), teriparatide (biosimilar formulation), generic teriparatide, and teriparatide (Forteo)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Member will not have received treatment with a parathyroid hormone for more than two years during their lifetime; **OR**
      1. Member will have received treatment with a parathyroid hormone for more than two years during their lifetime; **AND**
         i. Provider attestation that patient remains, or has returned to, having high or very high fracture risk (e.g., a fracture in the past 12 months, a fracture while on osteoporosis therapy, a history of multiple fractures, fractures while on long-term glucocorticoids, T-score ≤ -3.0, high risk for falls or a history of injurious falls, a FRAX 10-year probably for major fracture >30% or hip fracture >4.5%, etc.); **AND**

C. Medication will not be used in combination with other osteoporotic agents [e.g., denosumab (Prolia), bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid injection), calcitonin nasal spray, or raloxifene]; **AND**
D. One of the following fracture risk categories is met:
    1. Member has a fracture of the hip or spine regardless of BMD; **OR**
    2. Member has a T-score ≤ -2.5 in spine, femoral neck, total hip or 1/3 radius; **OR**
    3. Member has a T-score ≤ -1 and a history of recent fracture of proximal humerus, pelvis, or distal forearm; **OR**
    4. Member has a T-score between -1 and -2.5 with a FRAX 10-year probability for major fracture ≥20% or hip fracture ≥3%; **AND**
E. Provider attestation or clinical of treatment failure or ineffective response to <u>one</u> of the following, unless all are contraindicated (*Please note: These agents may be subject to prior authorization or step therapy and may require an additional review):
    1. Oral bisphosphonate (e.g., alendronate, ibandronate), **OR**
    2. Intravenous bisphosphonate (e.g., zoledronic acid injection*); **OR**
    3. Denosumab (Prolia)*; **AND**
F. For abaloparatide (Tymlos), a diagnosis of one of the following:
    1. **Post-Menopausal Osteoporosis in Women; OR**
    2. **Primary Osteoporosis/Hypogonadal-related Osteoporosis in Men; OR**
G. For teriparatide (biosimilar formulation), a diagnosis of one of the following:
    1. **Post-Menopausal Osteoporosis in Women; OR**
    2. **Primary Osteoporosis/Hypogonadal-related Osteoporosis in Men; OR**
    3. **Glucocorticoid-induced Osteoporosis; OR**
H. For generic teriparatide, a diagnosis of one of the following:
    1. **Post-Menopausal Osteoporosis in Women; AND**
        i. Treatment with abaloparatide (Tymlos) AND teriparatide (biosimilar formulation) have been ineffective, not tolerated, or contraindicated; **OR**
    2. **Primary Osteoporosis/Hypogonadal-related Osteoporosis in Men; AND**
        i. Treatment with abaloparatide (Tymlos) AND teriparatide (biosimilar formulation) have been ineffective, not tolerated, or contraindicated; **OR**
    3. **Glucocorticoid-induced Osteoporosis; AND**
        i. Member is taking ≥ 5 mg prednisone or its equivalent daily with an anticipated duration of ≥ 3 months; **AND**
        ii. Treatment with teriparatide (biosimilar formulation) has been ineffective, not tolerated or contraindicated; **OR**
I. For BRAND teriparatide (Forteo), a diagnosis of one of the following:
    1. **Post-Menopausal Osteoporosis in Women; AND**
        i. Treatment with abaloparatide (Tymlos), teriparatide (biosimilar formulation) AND generic teriparatide have been ineffective, not tolerated, or contraindicated; **OR**
    2. **Primary Osteoporosis/Hypogonadal-related Osteoporosis in Men; AND**
        i. Treatment with abaloparatide (Tymlos), teriparatide (biosimilar formulation) AND generic teriparatide have been ineffective, not tolerated, or contraindicated; **OR**

3. **Glucocorticoid-induced Osteoporosis; AND**
    i. Member is taking ≥ 5 mg prednisone or its equivalent daily with an anticipated duration of ≥ 3 months; **AND**
    ii. Treatment with teriparatide (biosimilar formulation) AND generic teriparatide has been ineffective, not tolerated or contraindicated

II. Parathyroid hormones are considered investigational when used for all other conditions, including but not limited to:
    A. Osteoporosis prophylaxis
    B. Promote fracture healing
    C. Promote post-fusion healing
    D. The use of abaloparatide (Tymlos) for glucocorticoid-induced osteoporosis.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication will not be used in combination with other osteoporotic agents [e.g., denosumab (Prolia), bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid injection), calcitonin nasal spray, or raloxifene]; **AND**
IV. If the request is for BRAND teriparatide (Forteo), treatment with teriparatide (biosimilar formulation) and generic teriparatide has Negat; **AND**
V. If the request is for generic teriparatide, treatment with teriparatide (biosimilar formulation) has been ineffective, not tolerated or contraindicated; **AND**
VI. Member has not received treatment with parathyroid hormone for more than a total of two years during their lifetime; **AND**
    A. Provider attestation that member has demonstrated clinical improvement or stability of osteoporosis (e.g., stable, or improved bone mineral density (BMD), reduction in or no new fracture(s), reduction in fracture risk) with parathyroid hormone therapy; **OR**
VII. Member will have received treatment with a parathyroid hormone for more than two years during their lifetime; **AND**
    A. Provider attestation that patient remains or has returned to having high or very high fracture risk (e.g., a fracture while on osteoporosis therapy, a history of multiple fractures, fractures while on long-term glucocorticoids, T-score ≤ -3.0, high risk for falls or a history of injurious falls, a FRAX 10-year probably for major fracture >30% or hip fracture >4.5%, etc.)

Supporting Evidence

I. Osteoporosis is characterized by decreased bone mass and increased fracture risk, most commonly at the spine, hip, and wrist. The definition of osteoporosis with high risk of fracture is defined for men and women as BMD T-score of spine, femoral neck, and/or total hip <-2.5 without fracture, having history of hip or vertebral fracture regardless of BMD, T-score ≤ -1 and

a history of recent fracture of proximal humerus, pelvis, or distal forearm, T-score between -1.0 and -2.5 in the spine, femoral neck, or total hip with a -20% 10-year FRAX risk of any fracture or -3% risk of hip fracture, and receiving long-term glucocorticoid doses greater than or equal to prednisone 7.5mg per day. Although BMD is a surrogate marker, meta-analyses have found that treatment-related changes in BMD after 24 months were significantly associated with hip, vertebral, and nonvertebral fracture risk reduction in men and women with osteoporosis. Bone turnover markers (BTM) also reflect the pharmacological response to osteoporosis therapies and decline in BTM largely contributes to antifracture effect. It is suggested that BTM is used in clinical studies to compliment BMD in assessing pharmacological response to treatment.

II. The maximum duration of use for parathyroid hormone agents (e.g., abaloparatide, teriparatide) is two years. As of November 2021, the safety and efficacy of these therapies remains undetermined. Treatment guidelines [e.g., Endocrine Society, American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE), American College of Rheumatology (ACR)] continue to recommend that use of parathyroid analogs be limited to 2 years. If further therapy is warranted, transition to bisphosphonates, denosumab, or raloxifene should be considered to maintain bone density gains experienced from PTH agents.
    A. In November 2020, teriparatide (Forteo) prescribing information was revised to indicate that use beyond two years may be considered if the patient remains, or has returned to, having high fracture risk. The black box warning for high risk of osteosarcoma was removed based on the results of three retrospective claims studies that did not indicate an increased risk of osteosarcoma associated with the use of teriparatide (Forteo). At this time, it is recognized that there is conflicting evidence for increased osteosarcoma risk with PTH therapies; however, there remains lack of evidence for safety and efficacy beyond two years of therapy. Further research is needed to determine the risk/benefit profile and medical necessity of extended therapy.
    B. It is reasonable to consider extending duration of therapy beyond two years in patients who remain, or have returned to, having high or very high fracture risk when benefits of extended therapy outweigh the risks. Examples of this patient population may include, but are not limited to, a fracture while on osteoporosis therapy, a history of multiple fractures, fractures while on long-term glucocorticoids, T-score ≤ -3.0, high risk for falls or a history of injurious falls, a FRAX 10-year probably for major fracture >30% or hip fracture >4.5%, etc.

III. There is lack of head-to-head trials evaluating comparative efficacy and safety of PTH analogs, teriparatide (Forteo), teriparatide biosimilar, and abaloparatide (Tymlos). Therefore, clinical superiority of one agent over the other is not established at this time. All PTH analogs have been evaluated against placebo and were found to increase BMD and/or reduce fracture risk, depending on the indication. Given the known safety, efficacy, and cost-effectiveness, trial of abaloparatide (Tymlos) is required prior to use of teriparatide biosimilar and teriparatide (Forteo) in the indicated populations.

IV. **Post-Menopausal Osteoporosis in Women:**
    A. The safety and efficacy of once-daily teriparatide (Forteo) and teriparatide, with a median exposure to treatment of 19 months, was examined in a double-blind, multicenter, placebo-controlled clinical study of 1637 postmenopausal women with osteoporosis (FORTEO 20 mcg, n=541). The absolute risk reduction for new fracture in

favor of teriparatide (Forteo) was a 9.3% reduction in vertebral fracture: 95% CI (5.5 – 13.1).

B. The safety and efficacy of abaloparatide (Tymlos) was evaluated in an 18-month, randomized, multicenter, double-blind, placebo-controlled clinical trial in postmenopausal women aged 49 to 86 years (mean age of 69) who were randomized to receive abaloparatide (Tymlos) 80 mcg (N = 824) or placebo (N = 821). The absolute risk reduction for fractures in favor of abaloparatide (Tymlos) was 3.6% reduction in vertebral fractures: 95% CI (2.1 – 5.4).

C. The 2020 AACE/ACE guidelines treatment recommendations are as follows:
   i. Initial treatment for high fracture risk: alendronate, denosumab, risedronate, or zoledronate (strong recommendation, high quality evidence)
   ii. Treatment for very-high fracture risk or patients, who cannot tolerate or adhere to oral bisphosphonates: zoledronate, abaloparatide, denosumab, romosozumab, teriparatide, and (strong recommendation, high quality evidence).
   iii. Follow-up treatment after parathyroid hormone: bisphosphonate or denosumab

D. Additionally, the 2020 Endocrine Society guidelines recommend bisphosphonates as initial treatment for high-risk patients, while denosumab may be considered as an alternative initial treatment (strong recommendation, high quality evidence). For patients with a very high risk of fracture, teriparatide and abaloparatide are recommended (strong recommendation, moderate quality evidence). It is recommended that antiresorptive therapies follow treatment with parathyroid hormones.

E. The majority of efficacy and safety data for the recommended pharmacologic treatments of postmenopausal osteoporosis are rooted in trials of bisphosphonates, which have reported robust long-term efficacy and relative safety. Similarly, denosumab (Prolia) has well established long-term safety and efficacy as an initial treatment option. Alternatively, recommendations for use of parathyroid hormone therapy in the first-line setting for patients with severe osteoporosis or very high fracture risk are primarily supported only by Phase 3 studies that compared teriparatide to bisphosphonates: NCT00051558, NCT00343252 and the VERO study. While these studies showed statistically significant improvements with teriparatide in surrogate markers related to osteoporosis (e.g., BMD changes, reduction in pain severity, and incidence of vertebral fracture) when compared to a bisphosphonate, they are confounded due to factors such as small sample sizes, high dropout rates, and high previous exposure to bisphosphonates. Additionally, clinical meaningfulness remains uncertain due to lack of longer-term applicability to broader osteoporosis population, and lack of outcomes related to long-term morbidity; thus, the overall quality of evidence is considered low to moderate and may not be sufficient to drive clinical decisions. As such, weighing the safety, efficacy, cost, and clinical experience, oral and intravenous bisphosphonates and denosumab (Prolia) are considered standard and appropriate high-value treatment options in this setting.

V. **Primary Osteoporosis/Hypogonadal-related Osteoporosis in Men**

A. The safety and efficacy of once-daily teriparatide (Forteo) and teriparatide injection was examined in a double-blind, multicenter, placebo-controlled clinical study of 437 men

with either primary (idiopathic) or hypogonadal osteoporosis (n=151) for a median exposure of 10 months. Patients were included if they were 30-85 years old, ambulatory, free of chronic conditions and lumbar or proximal spine BMD of at least 2 standard deviations below the average. Baseline characteristics were similar in all groups: mostly 99% white, average age 59 years, BM 25kg/m2, and average lumbar BMD T-score -2.2. The primary endpoint, change in lumbar spine bone mass density (BMD) from baseline, was met in 94% of men treated. Fifty-three percent of patients treated with teriparatide (Forteo) achieved at least a 5% increase in spine BMD, and fourteen percent of patients gained ≥10% in spine BMD.

B. The safety and efficacy of once-daily abaloparatide (Tymlos) was examined in a 12-month double-blind, multicenter, placebo-controlled clinical study with 228 men with primary or hypogonadal osteoporosis with high risk of fracture. The primary endpoint was percent change in lumbar spine BMD from baseline at 12 months. Men 40-85 years old were included if they had a diagnosis of osteoporosis (T-scores ≤ -2.5 and > -3.5 at the lumbar spine, total hip, or femoral neck, >65 years of age with BMD T-scores ≤ −2.0 (based upon the male reference database) and stable hydroxyvitamin D levels. Baseline characteristics were similar across both groups: mean age 68.3 years, mean lumbar spine BMD T-score -2.1, mean BMI 26.5 kg/m2, 56.6% of patients had prior fractures. The mean change in BMD at lumbar spine at 12 months for the abaloparatide (Tymlos) group was 8.48% compared to placebo, 1.17% ($p<0.001$). No new safety concerns with abaloparatide (Tymlos) were observed and several of the most frequently reported AEs in men were also among the most frequent previously reported in the ACTIVE study in women (dizziness, arthralgia, upper respiratory tract infection, headache, hypertension, and nasopharyngitis).

C. According to the 2020 AACE/ACE guidelines, first-line treatment for men with osteoporosis are bisphosphonates and denosumab may be considered as an alternative initial treatment (strong recommendation, high quality evidence). Selection of therapy is based on individualized factors such as gastrointestinal problems and concomitant androgen deprivation therapy. The National Osteoporosis Foundation (NOF), Endocrine Society, and AACE/ACE guidelines recommend that alendronate, risedronate, zoledronate and denosumab have evidence for “broad-spectrum” antifracture efficacy and should be, in the absence of contraindications, be considered as first line therapy in treatment of osteoporosis. According to the 2012 Endocrine Society guidelines, it is recommended that initial treatment of osteoporosis in men with recent hip fracture should receive zoledronic acid (strong recommendation, low quality evidence), while men with high fracture risk on testosterone should receive an effective anti-fracture agent such as a bisphosphonate or teriparatide (conditional recommendation, low quality evidence). Teriparatide (Forteo) is recommended in treatment of men and women with osteoporosis with upper or lower gastrointestinal problems, when nonoral therapy is preferred, or when patients cannot tolerate or do not respond adequately to bisphosphonates. Guidelines have not been updated to include abaloparatide (Tymlos) in therapy recommendations in men with osteoporosis.

D. The guidelines note that there is increasing evidence to support that BMD gains may be greater when an anabolic drug is administered before the antiresorptive drug compared

with the opposite sequence in patients with high-risk fracture. The 2022 NOF guidelines states that when sequential treatment is considered in patients with recent fractures and/or very low BMD (e.g., T-score < − 3.0), starting with anabolic therapy following an antiresorptive agent is preferred. The 2020 AACE/ACE guidelines also note that it probably is not advisable to use teriparatide (or abaloparatide) if denosumab is stopped. It is hypothesized that bone resorption is required, in part, for PTH analogs to stimulate new bone formation. If antiresorptive agents are suppressing bone resorption, the anabolic action of PTH analogs may be impaired. Although the 2022 NOF and 2020 AACE/ACE guidelines note that sequential therapy (anabolic preceding antiresorptive) may be considered in patients with recent fractures and/or very low BMD, the quality of evidence supporting this statement is low. There are three low quality studies which explored the question of sequential therapy. The studies should not be used for medical decision making due to small study populations, lack of blinding, lack of adherence assessment, and inconsistent BMD outcomes. More research is necessary to determine efficacy and appropriateness of sequential therapy at this time.

i. The DATA-switch study (Leder et al) was a randomized cross over study investigating the effect of sequential osteoporosis therapy in BMD in 77 postmenopausal women, 45 years or older, with osteoporosis. Participants were randomized 1:1:1 to receive teriparatide 20 mcg daily for 24 months then switched to denosumab 60mg every 6 months, denosumab every 6 months for 24 months then switched to teriparatide daily, or denosumab and teriparatide for 24 months, then switched to denosumab every 6 months. BMD at the spine, hip, and wrist were measured at 6, 12, 18, and 24 months after switching therapy. The primary endpoint, percent change in spine BMD over 4 years, was not statistically significant between all three groups (18.3%, 14.0% and 16.0%, p=0.13). The secondary outcome, hip BMD increase, was greater in the teriparatide to denosumab group (6.6%, 95% CI 5.3-7.9) compared to denosumab to teriparatide (2.8%, 95% CI 1.3-4.2), p=0.0002. After 48 months, radius bone mineral density was unchanged in the teriparatide to denosumab group (0.0% [95% CI -1.3 to 1.4]), whereas it decreased by -1.8% (-5.0 to 0.3), p=0.0075, in the denosumab to teriparatide group, and increased by 2.8% (1.2-4.4), p=0.0099, in the combination to denosumab group.
    a. The study is of low quality with concerns regarding validity of results due to open label study design, and a small size of the population studied. The primary endpoint did not meet statistical significance and the results of the secondary endpoints were inconsistent. Therefore, specific clinical impact of the transient bone loss that occurs in women switching from denosumab to teriparatide cannot be precisely estimated.

II. The DATA-Switch HR-pQCT study (Tsai et al) assessed the effects of sequential therapy on bone microarchitecture and strength at the distal tibia and radius in the DATA-Switch population. Study results found that women switching from teriparatide to denosumab had an increase in tibial BMD (net 48-month change -0.8% ± 2.4%) and combination-to-denosumab groups (net 48-month changes +2.4% ± 4.1%) and decreased in the denosumab to teriparatide group (net 48-month

change -3.4% ± 3.2%, p<0.001). Changes in total volumetric BMD followed similar patterns. Tibial cortical porosity increased in the denosumab-to-teriparatide group (+16.2% ± 11.5%, p <0.05 versus other groups).

a. The study is of low quality with concerns regarding validity of results due to open label study design and a small size of the population studied. Guidelines recommend that when spine and hip BMD are not evaluable, distal radius may be evaluated for initiation of therapy or therapy monitoring. Spine fractures are more common than hip and radius fractures. Hip fractures typically result in more severe outcomes such as increase in one-year mortality rate and loss of independence. Tibial BMD change and porosity trends may demonstrate changes in microarchitecture that influence bone strength at the tibia. However, tibia BMD values are not typically measured at baseline and there is uncertain applicability and value of these study results.

III. A European open-label, prospective, randomized trial (Obermayer-Pietsch, et al) evaluated the efficacy of osteoporosis sequential treatment regimens in 503 postmenopausal women with osteoporosis who received 24 months of teriparatide. The participants were divided into three groups based on prior antiresorptive treatment (treatment naïve, N=84, pretreated with no evidence of inadequate response to antiresorptive treatment, N=134, and pretreated with inadequate response, N=285). The majority of patients previously treated with antiresorptive treatment were treated with bisphosphonates, most commonly alendronate (86.6% and 93.0%). The primary endpoint was change in BMD at lumbar spine and secondary endpoints were changes in total hip BMD and femoral neck BMD. The mean gain in lumbar BMD was greater in the treatment naïve group (13.1%) compared to the pretreated without response (10.2%, p<0.005) and pretreated with inadequate response (9.8%, p<0.001). The mean gain in total hip BMD were 3.8%, 2.3%, and 2.3%, respectively. The difference in femoral neck BMD between the treatment-naïve and the inadequate responder subgroups was significant after 12 months, however, the mean changes were not significantly different across the three groups at 24 months (4.8%, 3.4%, 3.9%). The study concluded that the prior antiresorptive treatment blunted the BMD response to teriparatide.

a. There is low confidence in the study as it was open label, adherence was not addressed, and clinically meaningful differences in change of BMD is currently unknown, therefore it is difficult to draw conclusions. Additionally, confidence in study results is uncertain as the results in change in BMD across lumbar spine, total hip and femoral neck are inconsistent. The study showed increase in BMD at lumbar spine and hip, but no statistical difference at the femoral neck. Limitations in the study precludes drawing conclusions regarding sequential therapy.

VI. **Glucocorticoid-induced osteoporosis:**

A. The efficacy of teriparatide (Forteo) and teriparatide injection was assessed in a randomized, double blind, active-controlled trial of 428 patients (19% men, 81% women) aged 22 to 89 years (mean 57 years) treated with ≥ 5 mg/day prednisone or equivalent

for a minimum of 3 months. The duration of the trial was 18 months with 214 patients exposed to teriparatide (Forteo). In patients treated with teriparatide (Forteo), the mean percent change in BMD from baseline to endpoint was 7.2% at the lumbar spine, 3.6% at the total hip, and 3.7% at the femoral neck ($p<0.001$ all sites).

B. According to the 2017 ACR guidelines, in adults with glucocorticoid-induced osteoporosis regardless of fracture risk, initial treatment should include oral bisphosphonates. In patients who had a fracture in the past 18 months or lost >10% bone density per year, IV bisphosphonates, teriparatide, or denosumab be used in the second-line setting; in patients who remain at moderate-to-high fracture risk, treatment should continue with a bisphosphonate, or may be switched to an alternative class (conditional recommendation, low quality of evidence).

Investigational or Not Medically Necessary Uses

I. Osteoporosis Prophylaxis
   A. There is currently no evidence to support the use of parathyroid hormones for the prevention of postmenopausal osteoporosis.

II. Promote fracture healing and/or post fusion healing
   A. There is limited safety and efficacy evidence to support the use of parathyroid hormones in the setting of fracture healing and/or post fusion healing.

III. Abaloparatide (Tymlos) is only FDA-approved for the treatment of postmenopausal osteoporosis and primary/hypogonadal-related osteoporosis in men; there is currently a lack of sufficient evidence regarding safety and efficacy in other settings.

References

1. Forteo [Prescribing Information]. Indianapolis, IN: Eli Lilly and Company. September 2021.
2. Tymlos [Prescribing Information]. Waltham, MA: Radius Health, Inc. April 2021.
3. Teriparatide [Prescribing Information]. Morristown, NJ: Alvogen, Inc. November 2019.
4. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis-2020 update. *Endocr Pract*. 2020;26(Suppl 1):1-46.
5. Shoback D, Rosen CJ, Black DM, Cheung AM, Murad MH, Eastell R. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society guideline update. *J Clin Endocrinol Metab*. 2020;105(3):dgaa048.
6. Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;97(6):1802-1822.
7. Buckley L, Guyatt G, Fink HA, et al. 2017 American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Rheumatol*. 2017;69(8):1521-1537.
8. Saag KG, Shane E, Boonen S, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. *N Engl J Med.* 2007;357(20):2028-2039.
9. Hadji P, Zanchetta JR, Russo L, et al. The effect of teriparatide compared with risedronate on reduction of back pain in postmenopausal women with osteoporotic vertebral fractures. *Osteoporos Int.* 2012;23(8):2141-2150.
10. Kendler DL, Marin F, Zerbini CAF, et al. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (Vero): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet*. 2018;391(10117):230-240.
11. Miller PD, Lewiecki EM, Krohn K, Schwartz E. Teriparatide: Label changes and identifying patients for long-term use. *CCJM*. 2021;88(9):489-493.
12. Czerwinski E, Cardona J, Plebanski R, et al. The Efficacy and Safety of Abaloparatide-SC in Men With Osteoporosis: A Randomized Clinical Trial [published online ahead of print, 2022 Oct 3]. J Bone Miner Res. 2022;10.1002/jbmr.4719.

13. Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012;97(6):1802-1822.
14. LeBoff MS, Greenspan SL, Insogna KL, et al. The clinician's guide to prevention and treatment of osteoporosis [published correction appears in Osteoporos Int. 2022 Jul 28;:]. Osteoporos Int. 2022;33(10):2049-2102.
15. Leder BZ, Tsai JN, Uihlein AV, et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. Lancet. 2015;386(9999):1147-1155.
16. Tsai JN, Nishiyama KK, Lin D, et al. Effects of Denosumab and Teriparatide Transitions on Bone Microarchitecture and Estimated Strength: the DATA-Switch HR-pQCT study [published correction appears in J Bone Miner Res. 2019 May;34(5):976]. J Bone Miner Res. 2017;32(10):2001-2009.
17. Finkelstein JS, Wyland JJ, Lee H, Neer RM. Effects of teriparatide, alendronate, or both in women with postmenopausal osteoporosis. J Clin Endocrinol Metab. 2010;95(4):1838-1845.
18. Obermayer-Pietsch BM, Marin F, McCloskey EV, et al. Effects of two years of daily teriparatide treatment on BMD in postmenopausal women with severe osteoporosis with and without prior antiresorptive treatment. J Bone Miner Res. 2008;23(10):1591-1600.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy

Policy Name	Disease state
denosumab (Prolia)	Post-menopausal Osteoporosis in Women
	Osteoporosis in Men
	Increase Bone Mass in Women with Breast Cancer receiving Aromatase Inhibitor Therapy
	Increase Bone Mass in Men with Non-metastatic Prostate Cancer receiving Androgen Deprivation Therapy
	Glucocorticoid-induced Osteoporosis

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated criteria of treatment failure with bisphosphonates or Prolia to allow attestation and removed minimum 12-month trial requirement.	03/2024
Added generic teriparatide to policy with step through teriparatide (biosimilar formulation) and abaloparatide (Tymlos).	02/2024
Updated dosage forms to be reflective of product availability rather than concentration.	11/2023
Updated initial criteria requiring trial of abaloparatide (Tymlos) and teriparatide (biosimilar formulation) prior to brand Forteo. Updated renewal of brand Forteo to require teriparatide (biosimilar formulation) or abaloparatide (Tymlos).	02/2023
Updated criteria to include abaloparatide (Tymlos) in treatment of primary/hypogonadal-related osteoporosis in men. Included criteria regarding fractures despite BMD changes under fracture risk category. Removed primary/hypogonadal-related osteoporosis from investigational section. Added supporting evidence for new indication in osteoporosis in men and sequential therapy. Added related policies section.	12/2022
Added initial and renewal criteria for use beyond two years to demonstrate fracture risk remains high, refined diagnosis criteria to target patients with high fracture risk, and adjusted previous medication trials to require PO, IV bisphosphonate or Prolia while removing raloxifene and calcitonin. Updated and reformatted supporting evidence for limitation on duration of use and requirement of bisphosphonates or Prolia.	12/2021
Added criteria for the biosimilar teriparatide, requiring trial of the biosimilar prior to brand Forteo	11/2020
Added detail around maximum duration of approval [26 (monthly) fills] in order to provide more clarity around fill history. Addition of supporting evidence regarding maximum two year treatment duration	04/2020
Added in fill count to renewal duration, as well as updated to reflect a 28-day supply instead of 30-days in the Forteo QL table	02/2020
Criteria transitioned into policy format with the following additions: supporting evidence, investigational section, and a list of drugs that should not be used in combination with parathyroid hormones. Guidelines reviewed, and the following updates were made: differentiate between T-scores without fragility fracture	12/2019

and with fragility fracture, defined high risk fractures, and provided inclusion criteria for glucocorticoid-induced osteoporosis.	
Update criteria to include abaloparatide (Tymlos)	08/2017
Reviewed	10/2005, 01/2007, 12/2008, 06/2013, 02/2016, 06/2017, 12/2019
Date effective	03/2016
Policy created	09/2005

Policy Type: PA/SP Pharmacy Coverage Policy: UMP235

Description

Pegcetacoplan (Empaveli) is a subcutaneous complement inhibitor of C3. Iptacopan (Fabhalta) is an oral complement factor B inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
pegcetacoplan (Empaveli)	Paroxysmal nocturnal hemoglobinuria (PNH)	1,080 mg/20 mL vial	160 mL (8 vials)/28 days
iptacopan (Fabhalta)		200 mg capsules	60 capsules/30 days

Initial Evaluation

I. **Pegcetacoplan (Empaveli)** and **iptacopan (Fabhalta)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a hematologist or immunologist; **AND**
   C. Provider attestation that therapy will not be used in combination with other complement inhibitor therapy (e.g., eculizumab [Soliris], ravulizumab [Ultomiris]) (Note: overlapping therapy to comply with switch therapy guidance from anti-C5 therapy is allowed, *see Appendix*); **AND**
   D. Provider attestation of a diagnosis of **paroxysmal nocturnal hemoglobinuria** (**PNH**) confirmed via flow cytometry with PNH clones of at least 10%; **AND**
   E. Member has at least one of the following indications for treatment:
      1. Transfusion dependence (hemoglobin is 7 g/dL or less)
      2. Hemoglobin is 9 g/dL or less with symptoms of anemia (e.g. disabling fatigue)
      3. The member has experienced a thromboembolic event
      4. Presence of organ damage secondary to chronic hemolysis (e.g., renal insufficiency, pulmonary insufficiency/hypertension)
      5. High LDH activity (≥ 1.5 x ULN) with clinical symptoms
      6. Patient has symptoms associated with smooth muscle dystonia (e.g., abdominal pain, dysphagia, esophageal spasm, erectile dysfunction); **AND**
   F. The request is for pegcetacoplan (Empaveli); **OR**
      1. The request is for iptacopan (Fabhalta); **AND**
         i. Documentation that treatment with pegcetacoplan (Empaveli) has been ineffective, contraindicated, or not tolerated.

II. Pegcetacoplan (Empaveli) and iptacopan (Fabhalta) are considered investigational when used for all other conditions, including but not limited to:
   A. Paroxysmal nocturnal hemoglobinuria in pediatric patients
   B. Paroxysmal nocturnal hemoglobinuria in combination with other complement inhibitors
   C. Amyotrophic lateral sclerosis (ALS)
   D. Glomerulopathy or glomerulonephritis
   E. Macular degeneration
   F. Hemolytic uremic syndrome
   G. Myasthenia gravis
   H. Neuromyelitis optica spectrum disorder (NMOSD)
   I. Thrombotic microangiopathy
   J. IgA nephropathy
   K. Immune thrombocytopenia
   L. Immunoglobulin A (IgA) vasculitis (Henoch-Schoenlein purpura) in pediatric patients
   M. Immunoglobulin A (IgA) nephropathy

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Provider attestation that medication will not be used in combination with other complement inhibitor therapy (e.g., eculizumab [Soliris], ravulizumab [Ultomiris]); **AND**
IV. Member has exhibited improvement or stability of disease symptoms (e.g., increased hemoglobin, reduction in LDH, reduction in reticulocyte count, reduction in transfusion frequency)

Supporting Evidence

I. Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disease characterized by complement-mediated hemolysis, leading to debilitating fatigue, anemia, dyspnea, bone pain, bleeding/bruising, thrombosis, and bone marrow dysfunction. Curative therapy for PNH is allogenic hematopoietic stem cell (HSC) transplant; however, given safety and cost limitations, transplant is reserved for those with severe and refractory disease manifestations.
II. Diagnosis and treatment of this condition is highly specialized. To ensure appropriate diagnosis and that benefits of treatment outweigh risks, prescribing by, or in consultation with, a specialist is required. Confirmation of diagnosis by Flow Cytometry is currently the most accepted method to confirm diagnosis of PHN; therefore, this is required given the rarity of PNH and to ensure medication is medically necessary. Of note the proportion of PNH III cells, which are cells completely missing GPI-anchored proteins on the cell surface, can be diluted by a recent transfusion or depleted due to a recent hemolytic crisis.
III. Pegcetacoplan (Empaveli) and iptacopan (Fabhalta) have not been evaluated in combination with other complement inhibitors. There is currently one open-label, single-arm, phase 2 trial that is evaluating the use of iptacopan (Fabhalta) and eculizumab (Soliris) combination use;

however, study results are not mature. Therefore, the efficacy and safety of combination use remains unknown at this time.

IV. Treatment for PNH is indicated when signs and symptoms are present with a diagnosis confirmed via flow cytometry. Signs and symptoms include transfusion dependence (defined as a Hgb ≤7 g/dL), symptoms of anemia with a Hgb ≤9 g/dL, thrombosis, organ dysfunction, and debilitating fatigue associated with hematologic lab values that are out of the normal range (e.g., low Hgb, increased LDH, etc.). Smooth muscle dystonia can occur due to hemolysis induced depletion of nitric oxide, and is associated with abdominal pain, dysphagia, erectile dysfunction, and esophageal spasm. Nitric oxide depletion or pulmonary emboli can also be associated with pulmonary hypertension in some patients. The chronic hemolysis and associated anemia experienced by PNH patients can lead to disabling fatigue along with acute and chronic kidney disease. Anemia, and therefore the need for transfusions, can be multifactorial with hemolysis, iron deficiency, and bone marrow failure all of which contribute to low Hgb levels. The increased risk of thrombosis in PNH has a variety of potential contributing factors to the hypercoagulability state including prothrombotic microparticles, high levels of free Hgb, complement activation, and the absence/deficiency of GPI-linked proteins.

V. The C5 inhibitors, eculizumab (Soliris) and ravulizumab (Ultomiris) (± supportive care), have become standard of care given their ability to improve disease manifestations. However, these only target intravascular hemolysis, leaving opportunity for extravascular hemolysis in the liver and spleen. Despite treatment, anemia and the need for continued blood transfusions may persist in some patients. For the majority of patients C5 inhibitors are successful treatment options as they have shown to improve Hg, LDH levels, reticulocyte count, and/or reduce transfusion frequency. The safety profile of these therapies is well established.

VI. **Pegcetacoplan (Empaveli)**

- Pegcetacoplan (Empaveli) is a C3 complement inhibitor and acts proximally to the complement cascade preventing intravascular and extravascular hemolysis. It is the first complement inhibitor that may be self-administered - via a subcutaneous infusion pump; although, therapy may also be administered by a healthcare provider. Therapy that is being administered by a healthcare professional should be billed through the member's medical benefit.
- To date, pegcetacoplan (Empaveli) has been evaluated in adult patients. Clinical trials are underway to evaluate the safety and efficacy of pediatric patients. Other therapies [e.g., ravulizumab (Ultomiris)] have been evaluated and are FDA-approved down to one month of age. Until sufficiently evaluated in pediatric patients, pegcetacoplan (Empaveli) should be reserved for the FDA-approved age group(s) given the availability of alternate avenues of care (e.g., other FDA-approved medications, enrolment in clinical trials).
- The pivotal trial for pegcetacoplan (Empaveli) was an open label, randomized, Phase 3 study in comparison to eculizumab (Soliris) (PEGASUS trial). Patients were 18 years of age or older, had a hemoglobin of less than 10.5 mg/dL (mean 8.7 g/dL) while on stable doses of eculizumab (Soliris) for at least three months before enrollment, 75% received a blood transfusion in the last year (over 50% of patients received four or more).
- Eighty patients were enrolled in the trial. Seventy-five percent had received a blood transfusion in the last year (over 50% of patients received four or more). Primary outcome: change in Hg from baseline at week 16. Secondary outcomes: proportion of transfusion-free patients, change in reticulocyte count, lactate dehydrogenase (LDH) level, and Functional Assessment of Chronic Illness Therapy-Fatigue Scale

(FACIT-F). The normalization of hematologic variables was also evaluated. Endpoints were tested in a hierarchical manner, the primary outcome was tested for superiority, and the secondary outcomes were tested for non-inferiority (NI). The primary outcome met superiority, and transfusion rate and reticulocyte count met NI. Normalization of hematologic variables (Hg, reticulocytes, LDH) were favorable for pegcetacoplan (Empaveli). Pegcetacoplan (Empaveli) was also evaluated in Phase 1 and 2 open-label, single-arm trials in complement inhibitor-naïve patients. Improvements were seen in Hg, LDH, reticulocytes, and FACIT-F scores in a small number of patients.

- The safety and efficacy of pegcetacoplan (Empaveli) has been established for 1,080 mg (20 mL) twice weekly. In the clinical trials, three patients discontinued therapy given lack of efficacy. Following, a protocol amendment was made to allow an increase in the dose to every three days, and two patients received the increased dose. Data regarding the safety and efficacy of 1,080 mg (20mL) three times a week has been proven in scientific literature, and the pegcetacoplan (Empaveli) prescribing information recommends adjusting the dosing to 1,080mg (20 mL) every three days for lactate dehydrogenase (LDH) levels greater than 2× the upper limit of normal (ULN).
- With the exception of the four-week overlap to get patients established on pegcetacoplan (Empaveli), therapy has not been evaluated in combination with other complement inhibitors. It is advised that complement inhibitors are not abruptly discontinued. If switching from eculizumab (Soliris), therapy should be overlapped for four weeks with pegcetacoplan (Empaveli). For those switching from ravulizumab (Ultomiris), pegcetacoplan (Empaveli) should be started no more than four weeks after the last dose of ravulizumab (Ultomiris). Maintenance therapy with more than one complement inhibitor therapy is not expected to have additional efficacy and is expected to have serious safety implications (e.g., serious infections caused by encapsulated bacteria). Thus, maintenance on more than one complement inhibitor therapy is not indicated at this time.
- The bulk of evidence is from patients that were refractory to C5 inhibitor, eculizumab (Soliris), and it is expected that pegcetacoplan (Empaveli) will be utilized heavily in this treatment setting; however, given the alternative protein target of this therapy, coupled with evidence data support from Phase 1 and 2 trials, it is expected pegcetacoplan (Empaveli) will be efficacious as a first-line treatment. A clinical trial is underway to evaluate this further.

VII. **Iptacopan (Fabhalta)**

- The safety and efficacy of iptacopan (Fabhalta) was evaluated in two Phase 3, multicenter, open-label trials. Both trials were studied in adult patients aged 18 years and older. Safety and efficacy has not been evaluated pediatric patients.
- The APPPLY-PNH trial was a 24-week multicenter, open-label, randomized, Phase 3 trial which compared iptacopan (Fabhalta) against standard of care (SOC), eculizumab (Soliris) or ravulizumab (Ultomiris), in adult patients with PNH, as evidenced by a diagnosis via high-sensitivity flow cytometry with a clone size ≥10% and a hemoglobin less than 10 g/dL. Patients were required to be on a stable dose of eculizumab (Soliris) or ravulizumab (Ultomiris) for at least 6 months prior to randomization and 56% of patients had received a blood transfusion in the 6 months prior to enrollment. The primary endpoint was the percentage of participants achieving a hematological response, defined as an increase from

baseline in Hb ≥2 g/dL in the absence of RBC transfusions, and demonstrated statistically significant change compared to SOC (difference: 80.3% [95% CI: 71.3-87.6]; p<0.0001). The other primary endpoint, percentage of participants achieving sustained Hb ≥12 g/dL in the absence of RBC transfusions, also demonstrated statistical significance compared to SOC (difference: 67.0% [95% CI: 56.3-76.9]; p<0.0001).

- The APPOINT-PNH trial was an open-label, single arm, Phase 3 trial that enrolled 40 treatment naïve, adult patients with a high-sensitivity flow cytometry clone size of ≥10%, Hgb <10 g/dL, and a LDH >1.5 ULN. The primary endpoint, percentage achieving hematological response, defined as an increase from baseline in Hb ≥2 g/dL in the absence of RBC transfusions, was met (92.2% (95% CI: 82.5-100)). One key secondary endpoint was percentage achieving hematological response defined as having Hb ≥12 g/dL in the absence of RBC transfusions, which was also met (62.8% (95% CI: 47.5-77.5)).
- The safety and efficacy of iptacopan (Fabhalta) has been established for 200mg capsules twice daily. In the APPLY trial 82.3% of patients experienced a TEAE as compared to 80% of the comparator group. The most common TEAEs in the iptacopan (Fabhalta) group were headache (16.1%), diarrhea (14.5%), and nasopharyngitis (11.3%). Serious TEAEs occurred in 9.7% of the iptacopan (Fabhalta) patients while 14.3% of patients in the comparator group experienced a serious TEAE. No patient in the iptacopan (Fabhalta) group experienced a hemolysis related serious TEAE while one patient in the comparator group experienced breakthrough hemolysis and another experienced extravascular hemolysis. No patients discontinued due to adverse events or deaths. In the APPOINT trial, no breakthrough hemolysis events or MAVEs were reported during the 24-week core treatment period. TEAEs were reported in 93% of patients with 65% considered mild in severity. The most common TEAEs were headache (27.5%), COVID-19 (15%), and upper respiratory tract infection (12.5%). Serious TEAEs were reported in 10% of patients with one case of bacterial pneumonia, COVID-19, type II diabetes mellitus, and cataract. No patients discontinued due to side effects and no deaths were reported.
- Both iptacopan (Fabhalta) and pegcetacoplan (Empaveli) have studies (APPLY-PNH and PEGASUS, respectively) demonstrating their efficacy in patients who were not clinically stable on anti-C5 therapy. There are no direct comparison trials available demonstrating superiority of iptacopan (Fabhalta) to pegcetacoplan (Empaveli), the use of the most cost-effective treatment option should be considered. For these reasons, trial of pegcetacoplan (Empaveli) is required prior to use of iptacopan (Fabhalta), unless contraindicated, not tolerated, or ineffective.

Investigational or Not Medically Necessary Uses

I. Pegcetacoplan (Empaveli) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Paroxysmal nocturnal hemoglobinuria in pediatric patients
   B. Paroxysmal nocturnal hemoglobinuria in combination with other complement inhibitors
   C. Amyotrophic lateral sclerosis (ALS)
   D. Glomerulopathy or glomerulonephritis

E. Macular degeneration
F. Hemolytic uremic syndrome
G. Myasthenia gravis
H. Neuromyelitis optica spectrum disorder

Appendix

I. Complement inhibitor administration:

Therapy	Dose/Frequency	Duration of medication coverage (maintenance)	Route
iptacopan (Fabhalta)	200 mg twice daily	1 day	PO
pegcetacoplan (Empaveli)	1,080 mg (20 mL) twice weekly	3-4 days	SQ
eculizumab (Soliris)	600 mg weekly for four weeks, 900 mg on the fifth week, then 900 mg every two weeks thereafter	2 weeks	IV
ravulizumab (Ultomiris)	One loading dose (based on weight) 2,400 mg-3,000 mg, then maintenance treatment (based on weight) starting two weeks later: 3,000 mg – 3,600 mg every eight weeks	8 weeks	IV

II. Switch therapy guidance:

- Transitioning from eculizumab (Soliris) to pegcetacoplan (Empaveli): Overlap therapy for four weeks (i.e., initiate pegcetacoplan [Empaveli] while continuing eculizumab [Soliris] at the current dose). Then, discontinue eculizumab (Soliris) after four weeks of treatment with pegcetacoplan (Empaveli) - to utilize pegcetacoplan (Empaveli) as monotherapy.
- Transitioning from ravulizumab (Ultomiris) to pegcetacoplan (Empaveli): Once the last dose of ravulizumab (Ultomiris) is administered, pegcetacoplan (Empaveli) should be initiated within four weeks of the infusion. No further doses of ravulizumab (Ultomiris) should be administered while pegcetacoplan (Empaveli) treatment is active.
- Transitioning from eculizumab (Soliris) to iptacopan (Fabhalta): initiate iptacopan (Fabhalta) no later than one week after the last dose of eculizumab (Soliris).
- Transitioning from ravulizumab (Ultomiris) to iptacopan (Fabhalta): initiate iptacopan (Fabahalta) no later than 6 weeks after the last dose of ravulizumab (Ultomiris).
- Transitioning from eculizumab (Soliris) to ravulizumab (Ultomiris) or vice versa: reference prescribing information for guidance.

References

1. Hillmen P, Szer J, Weitz I, et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2021;384(11):1028-1037.
2. Parker CJ. Update on the diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Hematology*. 2016(1):208-216.
3. Empaveli [Prescribing Information]. Apellis Pharmaceuticals, Inc. May 2021.
4. Apellis Pharmaceuticals, Inc. Phase Iia, Open Label, Multiple Dose Study to Assess the Safety, Efficacy and Pharmacokinetics of Subcutaneously Administered Apl-2 in Subjects with Paroxysmal Nocturnal Hemoglobinuria (Pnh). clinicaltrials.gov; 2020.

5. Apellis Pharmaceuticals, Inc. A Phase Ib, Open Label, Multiple Ascending Dose, Pilot Study to Assess the Safety, Preliminary Efficacy and Pharmacokinetics of Subcutaneously Administered Apl-2 in Subjects with Paroxysmal Nocturnal Hemoglobinuria (Pnh). clinicaltrials.gov; 2020.
6. Paroxysmal nocturnal hemoglobinuria. National Organization for Rare Disorders. January 5, 2023. Accessed November 30, 2023. https://rarediseases.org/rare-diseases/paroxysmal-nocturnal-hemoglobinuria/#complete-report.
7. Iptacopan (Fabhalta) dossier. Novartis. June 2023.
8. Empaveli. Package insert. Apellis Pharmaceuticals, Inc; 2023.
9. Fabhalta. Package insert. Novartis Pharmaceuticals Corporation; 2023.
10. Cançado RD, Araújo ADS, Sandes AF, et al. Consensus statement for diagnosis and treatment of paroxysmal nocturnal haemoglobinuria. *Hematol Transfus Cell Ther*. 2021;43(3):341-348. doi:10.1016/j.htct.2020.06.006
11. Pu JJ, Brodsky RA. Paroxysmal nocturnal hemoglobinuria from bench to bedside. *Clin Transl Sci*. 2011;4(3):219-224. doi:10.1111/j.1752-8062.2011.00262.x

Policy Implementation/Update:

Action and Summary of Changes	Date
Added iptacopan (Fabhalta) capsules to the policy. Updated supporting evidence and other investigational conditions.	02/2024
Policy created	08/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP183

Description

Peanut allergen powder-dnfp (Palforzia) is an oral immunotherapy FDA-approved for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. The mechanism of action is unknown at this time.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
peanut allergen powder-dnfp (Palforzia)	0.5 mg – 6 mg capsule sprinkle	Peanut allergy	13 capsule sprinkles/1 day
	3 mg daily dose capsule sprinkle		45 capsule sprinkles/15 days
	6 mg daily dose capsule sprinkle		90 capsule sprinkles/15 days
	12 mg daily dose capsule sprinkle		45 capsule sprinkles/15 days
	20 mg daily dose capsule sprinkle		15 capsule sprinkles/15 days
	40 mg daily dose capsule sprinkle		30 capsule sprinkles/15 days
	80 mg daily dose capsule sprinkle		60 capsule sprinkles/15 days
	120 mg daily dose capsule sprinkle		30 capsule sprinkles/15 days
	160 mg daily dose capsule sprinkle		60 capsule sprinkles/15 days
	200 mg daily dose capsule sprinkle		30 capsule sprinkles/15 days
	240 mg daily dose capsule sprinkle		60 capsule sprinkles/15 days
	300 mg titration powder pack		15 capsule sprinkles/15 days
	300 mg maintenance capsule sprinkle powder pack		30 capsule sprinkles/30 days

Initial Evaluation

I. Peanut allergen powder-dnfp (Palforzia) may be considered medically necessary when the following criteria are met:
   A. Member is four to 17 years of age and request is for initial dose escalation; **OR**
      1. Member is four years of age or older and is up-dosing; **AND**
   B. Medication is prescribed by, or in consultation with an allergist or immunologist; **AND**
   C. The medication will not used in combination with Viaskin™ Peanut patch or other peanut desensitization therapy; **AND**
   D. A diagnosis of **peanut allergy** when the following are met:
      1. Documented medical history of severe peanut allergy, with reactions that cannot be managed with conventional therapies such as antihistamines (e.g., reaction

causes anaphylaxis, requires epinephrine use, allergy that can be triggered by smell); **AND**

2. Must have current prescription for epinephrine; **AND**
3. Medication used in conjunction with peanut-avoidant diet; **AND**
4. Member does not have severe or uncontrolled asthma; **AND**
5. Member does not have eosinophilic esophagitis

II. Peanut allergen powder-dnfp (Palforzia) is considered investigational when used for all other conditions, including but not limited to:
   A. Initial dose escalation in members 18 years of age and older

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member is four to 17 years of age; **OR**
   A. Member is four years of age or older and is up-dosing or in maintenance; **AND**
IV. Must have current prescription for epinephrine; **AND**
V. Medication used in conjunction with peanut-avoidant diet; **AND**
VI. Member does not have severe or uncontrolled asthma; **AND**
VII. Member does not have eosinophilic esophagitis; **AND**
VIII. The medication will not used in combination with Viaskin™ Peanut patch or other peanut desensitization therapy

Supporting Evidence

I. The pivotal Phase 3 double-blind, placebo-controlled trial (PALISADE) leading to FDA-approval of peanut allergen powder-dnfp (Palforzia) consisted of 551 subjects aged 4 through 55 years with peanut allergy. However, the primary efficacy analysis population included only those aged 4-17 years as there were very few patients 18 years and older in the trial. Thus, FDA-approval is specific to patients aged 4 through 17 years, although Up-Dosing and Maintenance may be continued in patients 4 years of age and older. To date, there is insufficient evidence to support the initiation of peanut allergen powder-dnfp (Palforzia) therapy past the age of 17 years. Studies in adults are on-going.
II. In the PALISADE trial subjects had confirmed peanut allergy diagnosis consisting of a clinical history of peanut allergy and an elevated IgE test ($\geq$ 0.35 kUA/L) or positive skin test (mean wheal diameter $\geq$ 3 mm larger than negative control). To be included in the trial subjects must have also had a reaction to an oral food challenge with dose limiting symptoms to no more than 100 mg of peanut protein (~ one third of a peanut kernel). Oral food challenges are not routinely done in practice but may be needed if the patient's clinical history and IgE test results do not clearly indicate an allergy.

III. A confirmed allergy diagnosis consisting of a clinical history of allergy along with confirmatory values (elevated IgE, positive skin test, or food challenge) is utilized as per guideline recommendations. The 2010 Guidelines for the Diagnosis and Management of Food Allergy in the United States indicate, "because individuals can develop allergic sensitization (as evidenced by the presence of allergen-specific IgE (sIgE)) to food allergens without having clinical symptoms on exposure to those foods, an sIgE-mediated food allergy requires both the presence of sensitization and the development of specific signs and symptoms on exposure to that food. Sensitization alone is not sufficient to define food allergy".

IV. The peanut allergen powder-dnfp (Palforzia) package insert and Risk Evaluation and Mitigation Strategy (REMS) program require peanut allergen powder-dnfp (Palforzia) be used in conjunction with a peanut-avoidant diet and prescribed with injectable epinephrine. Additionally, the package insert carries a black box warning for anaphylaxis that further states treatment should not be administered in patients with uncontrolled asthma.

V. Peanut allergen powder-dnfp (Palforzia) carries a warning and precaution for eosinophilic esophagitis as cases of eosinophilic esophagitis occurred in clinical trials (13.7% of patients during dose escalation). Use in patients with a history of eosinophilic esophagitis is contraindicated per the package insert. Eosinophilic esophagitis is inflammation and increased numbers of eosinophils in the esophagus. It can cause feeding disorders, vomiting, reflux symptoms, and abdominal pain in children; and dysphagia and esophageal food impactions in adolescents and adults. Eosinophilic esophagitis is a known complication of oral immunotherapy.

VI. Viaskin™ Peanut patch is a peanut desensitization therapy under review by the FDA. Safety and efficacy of combination use of peanut desensitization therapy is unknown.

VII. An evidence report by the Institute for Clinical and Economic Review (ICER) states there is only moderate certainty of a comparable, small, or substantial net health benefit and a small (but non-zero) likelihood of a negative net health benefit for peanut allergen powder-dnfp (Palforzia) compared with strict avoidance and rapid use of epinephrine (PI, promising, but inconclusive). This is due to net health benefit being driven by changes in quality of life and reductions in reactions to accidental exposure to peanuts, neither of which has been demonstrated. Additionally, the increase in patients treated who were able to tolerate 600 mg of peanut protein (~2 peanut kernels) during the exit food challenge in the trial compared with those treated with placebo (67.2% vs. 4.0%) is balanced by a significant increase in gastrointestinal symptoms, systemic allergic reactions, and epinephrine use.

VIII. Use of peanut allergen powder-dnfp (Palforzia) is reserved for members with a history of severe peanut allergy. Due to the safety risks noted above coupled with the unknown clinical significance and meaningfulness of improving tolerance of a single dose of 600 mg peanut protein. How tolerance of 600 mg of peanut protein relates to changes in quality of life and reductions in reactions to accidental exposure to peanuts was not evaluated in the clinical trial.

Investigational or Not Medically Necessary Uses

I. Peanut allergen powder-dnfp (Palforzia) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Initial dose escalation in members 18 years of age and older

i. Though the PALISADE trial included subjects aged 4-55 years, the prespecified primary analysis population consisted of the subjects aged 4-17 years who received at least one dose of study drug (n=496). Efficacy in those who were 18 and older (n=55) was evaluated as a secondary endpoint but did not show statistical significance.
ii. FDA-approval is specific to patients aged 4 through 17 years, although Up-Dosing and Maintenance may be continued in patients 4 years of age and older. To date, there is insufficient evidence to support the initiation of peanut allergen powder-dnfp (Palforzia) therapy past the age of 17 years. Studies in adults are on-going.

References

1. Palforzia [Prescribing information]. Aimmune Therapeutics, Inc: Brisbane, CA. January 2020.
2. Vickery BP, Vereda A, Casale TB, et al. AR101 Oral Immunotherapy for Peanut Allergy. N Engl J Med. 2018;379(21):1991-2001.
3. Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update-2014. J Allergy Clin Immunol. 2014;134(5):1016-25.e43.
4. UpToDate, Inc. Investigational therapies for food allergy: Oral immunotherapy. UpToDate [database online]. Waltham, MA. Last updated Nov 25, 2019 Available at: http://www.uptodate.com/home/index.html.
5. UpToDate, Inc. Diagnostic evaluation of food allergy. UpToDate [database online]. Waltham, MA. Last updated Apr 23, 2019 Available at: http://www.uptodate.com/home/index.html.
6. Boyce JA, Assa'ad A, Burks AW, et al; NIAID-Sponsored Expert Panel. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010;126(suppl 6):S1-S58. doi: 10.1016/j.jaci.2010.10.007
7. Sampson HA, Gerth van wijk R, Bindslev-jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol. 2012;130(6):1260-74.
8. Institute for Clinical and Economic Review. Oral immunotherapy and Viaskin peanut for peanut allergy: Effectiveness and value. Published July 20, 2019. Available at: https://icer.org/news-insights/press-releases/final_report_peanut_allergy/.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP098

Description

Peginterferon alfa-2b (Sylatron) is a subcutaneous interferon which induces cellular activities related to binding specific cell-surface membrane receptors. These include suppression of cell proliferation, antiviral activity and immunomodulating effects.

Length of Authorization

- Initial: Eight weeks
- Renewal: 12 months, maximum of five years of therapy

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
peginterferon-alfa 2b (Sylatron)	200 mcg subcutaneous powder for solution	Adjuvant treatment of melanoma with microscopic or gross nodal involvement	4 vials/ 28 days
	300 mcg subcutaneous powder for solution		
	600 mcg subcutaneous powder for solution		

Initial Evaluation

I. Peginterferon alfa-2b (Sylatron) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with an oncologist; **AND**
   C. A diagnosis of **melanoma** when the following are met:
      1. The member has stage III disease; **AND**
      2. The member has microscopic or gross nodal involvement; **AND**
      3. The member has had definitive surgical resection including complete lymphadenectomy within the past 84 days (12 weeks); **AND**
      4. Peginterferon alfa-2b is prescribed as adjuvant treatment; **AND**
      5. The prescribed dose does not exceed 6 mcg/kg per week for the first eight weeks, then 3 mcg/kg per week thereafter; **AND**
      6. Attestation from the provider that the member does **not** have any of the following:
         i. Hepatic decompensation (Child-Pugh Score >6, class B and C)
         ii. Autoimmune hepatitis

iii. Depression or other neuropsychiatric disorders

II. Peginterferon-alfa 2b (Sylatron) is considered investigational when used for all other conditions, including but not limited to:
   A. Hepatitis C
   B. Cholangiocarcinoma
   C. Hematological malignancies
   D. Solid tumors and malignancies outside of melanoma

Renewal Evaluation

I. Member has not been established on therapy by the use of free samples, manufacturer coupons, or otherwise; **AND**
II. Member has received a previous prior authorization approval for this agent; **AND**
III. The medication is prescribed by or in consultation with an oncologist; **AND**
IV. Member has experienced response to treatment, such as stabilization of disease, decrease in disease spread, regression of disease; **AND**
V. The prescribed dose does not exceed 3 mcg/kg after the first eight weeks of therapy; **AND**
VI. Attestation from the provider that the member does **not** have any of the following:
   - Hepatic decompensation (Child-Pugh Score >6, class B and C)
   - Autoimmune hepatitis
   - Depression or other neuropsychiatric disorders

Supporting Evidence

I. Peginterfeon-alfa 2b (Sylatron) was evaluated in an open-label, randomized study of 1256 subjects with surgically resected stage III melanoma within 84 days (12 weeks) of regional lymph node dissection. The dose administered was 6 mcg/kg per week for eight weeks on average. Less than 1% received this dose for longer than nine weeks; thus, safety and efficacy for this dose for more than eight weeks is not FDA-approved and has not been sufficiently evaluated for safety and or efficacy.
II. Subjects were randomized to observation or peginterferon-alfa 2b (Sylatron) for up to five years. The primary outcome was relapse-free survival (RFS) or death from any cause, with overall survival (OS) as the secondary outcome. The RFS duration for peginterferon-alfa 2b (Sylatron) was 34.8 months versus 25.5 months for the observation arm. Safety and efficacy past five years of therapy has not been established, and OS benefits have not been established.
III. Peginterferon-alfa 2b (Sylatron) has a Black Box Warning for neuropsychiatric disorders, and may cause or aggravate severe depression or other psychiatric adverse events. Members with these conditions should only be started on therapy if the benefit outweighs the risks and should be monitored closely. Resolution of symptoms does not always occur upon discontinuation. Additionally, peginterferon-alfa 2b (Sylatron) is contraindicated in autoimmune hepatitis and those with hepatic decompensation.

IV. Vials of peginterferon-alfa 2b (Sylatron) are dose priced; therefore, vial size should be chosen to provide the appropriate dose and minimize waste.
V. As of November 2019, National Comprehensive Cancer Network treatment guidelines for cutaneous melanoma did not have recommendations for peginterferon-alfa 2b (Sylatron) in the setting of melanoma.

Investigational or Not Medically Necessary Uses

I. Peginterferon-alfa 2b (Sylatron) is not FDA-approved and has not been sufficiently evaluated for safety and/or efficacy in the following settings:
   A. Hepatitis C
   B. Cholangiocarcinoma
   C. Hematological malignancies
   D. Solid tumors and malignancies outside of melanoma

References

1. Sylatron [Prescribing Information]. Merck Sharp & Dohme Corp. Whitehouse Station, NJ. 2011.
2. NCCN Clinical Practice Guidelines in Oncology Cutaneous Melanoma. V3.2019. National Comprehensive Cancer Network. October 22, 2019. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx#melanoma.

Policy Implementation/Update:

Date Created	December 2012
Date Effective	January 2013
Last Updated	November 2019
Last Reviewed	11/2019

Action and Summary of Changes	Date
Prior authorization criteria transitioned to policy format. Criteria updated to include age edit, stage of disease, place in therapy, maximum dose. Renewal criteria updated to current format and language, added specialist requirement, contraindications, dose check. Change of initial duration of approval, change to maximum coverage of five years.	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP213

Description

Peginterferon alfa-2a (Pegasys) is a subcutaneous pegylated interferon which induces cellular activities related to binding specific cell-surface membrane receptors. These include suppression of cell proliferation, antiviral activity, and immunomodulating effects.

Length of Authorization

- Initial:
  - Chronic Hepatitis B: 48 weeks
  - All other indications: 12 months
- Renewal:
  i. For Polycythemia Vera AND Essential Thrombocythemia: 12 months
  ii. For all other indications: None

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
Peginterferon Alfa-2a (Pegasys; Pegasys ProClick)	180 µg/mL vial	Chronic Hepatitis B; Chronic Hepatitis D; Polycythemia Vera; Essential Thrombocythemia	4 vials/30 days
	180 µg/0.5 mL prefilled syringe		4 syringes/30 days
	135 µg/0.5 mL autoinjector		4 autoinjectors/30 days
	180 µg/0.5 mL autoinjector		4 autoinjectors/30 days

Initial Evaluation

I. **Peginterferon Alfa-2a (Pegasys)** may be considered medically necessary when the following criteria below are met:
   A. The medication is prescribed by, or in consultation with, a gastroenterologist, hepatologist, infectious disease specialist, hematologist, or an oncologist; **AND**
   B. The medication will be used as monotherapy; **AND**
   C. Member has not previously experienced disease progression while on peginterferon Alfa-2a (Pegasys) for the treatment of indications listed in this policy; **AND**
   D. Provider attestation that the member does **not** have any of the following:
      i. Hepatic decompensation (Child-Pugh Score> 6, Class B and C)
      ii. Autoimmune hepatitis
      iii. Depression or other neuropsychiatric disorders; **AND**
   E. A diagnosis of one of the following:
      1. **Chronic Hepatitis B; AND**
         i. Member is 3 to 17 years old; **AND**

a. Provider attests to **ALL** of the following:
    i. Member is hepatitis B e-antigen (HBeAg) positive; **AND**
    ii. Member is noncirrhotic; **AND**
    iii. Member has elevated serum alanine aminotransferase (ALT) more than twice the upper limit of normal (ULN); **OR**

ii. Member is 18 years of age or older; **AND**
    a. Documentation of hepatitis B (HBV) viral load less than 12 months old (i.e. serum HBV > 100,000 copies/mL or HBV DNA levels > 2000 IU/mL); **OR**

2. **Chronic Hepatitis D; AND**
    i. Diagnosis of chronic hepatitis D (HDV) confirmed by a quantifiable HDV RNA; **AND**
    ii. Provider attests the member has active liver disease (e.g. elevated serum ALT, or liver biopsy); **OR**
3. **Polycythemia Vera; OR Essential Thrombocythemia; AND**
    i. Member is 18 years of age or older; **AND**
    ii. Provider attests that the member has high-risk disease; **AND**
    iii. Treatment with generic hydroxyurea has been ineffective, contraindicated, or not tolerated

II. Peginterferon Alfa-2a (Pegasys) is considered not medically necessary when used for:
    A. Treatment of chronic hepatitis C (HCV)

III. Peginterferon Alfa-2a (Pegasys) is considered investigational when used for all other conditions, including but not limited to:
    A. Malignant melanoma
    B. Renal cell carcinoma
    C. Hairy cell leukemia
    D. Myelofibrosis
    E. Systemic mastocytosis
    F. Chronic myelogenous leukemia (CML)

Renewal Evaluation

I. Member has not been established on therapy by use of free samples, manufacturer coupons or otherwise; **AND**
II. Member has received previous prior authorization for this agent through THIS health plan; **AND**
III. Provider attestation that the member does **not** have any of the following:
    i. Hepatic decompensation (Child-Pugh Score> 6, Class B and C)
    ii. Autoimmune hepatitis
    iii. Depression or other neuropsychiatric disorders; **AND**
IV. Member has diagnosis of **Polycythemia Vera, or Essential Thrombocythemia; AND**

V. Member has experienced response to therapy such as disease stabilization or remission (e.g. complete or partial response)

Supporting Evidence

I. Interferons, a family of naturally occurring small protein molecules or glycoproteins, are produced by cells in response to viral infections or various synthetic or biologic inducers. Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Once bound to the cell membrane, interferons initiate a complex sequence of intracellular events. Interferons have been found to mediate antiviral, antiproliferative, and immunomodulatory activities. Peginterferon alfa-2a (Pegasys®) is a covalent conjugate of recombinant alfa-2a interferon. Other types of alfa interferon such as Peginterferon alfa-2b (PegIntron®, Sylatron™) are covered under separate PA policies based on their respective indications.

II. Given the treatment complexities associated with the indications listed in this policy, use of peginterferon alfa-2a (Pegasys) should be prescribed by a specialist practicing in the respective area of specialty.

III. Patients with chronic hepatitis B are at an increased risk to develop cirrhosis, liver failure, and liver cancer. Hepatitis B e-antigen (HBeAg) and Hepatitis B viral DNA (HBV DNA) are both markers of HBV replication and their presence provides a rationale for initiating therapy to stop the progression of liver disease. In the past, the ability to detect HBV DNA in the serum by hybridization assays was a major factor in determining which patients should be treated. This assay is sensitive enough to detect viral DNA when it is present in amounts ≥ 105 copies/ml and consequently this viral level became an important benchmark in treatment algorithms. As improvements in viral detection have advanced it has become apparent that it is not possible to designate a single HBV DNA value that can differentiate between inactive hepatitis B carriers and patients suffering from chronic hepatitis B.

IV. There are several agents currently indicated for treatment of chronic HBV. They include Peg-interferon, lamivudine, telbivudine, entecavir, tenofovir and adefovir. AASLD guidelines recommend peginterferon alfa-2a, entecavir, or tenofovir as preferred initial therapy for adults with immune-active chronic HBV infection. peginterferon alfa-2b is not FDA approved for chronic hepatitis B; however, there are studies that support its use for this indication. Overall, the quality of evidence is considered low for this setting.

V. Interferon therapy is not recommended in patients with decompensated cirrhosis because it increases their risk for developing bacterial infections and it can potentially worsen their condition.

VI. Peginterferon alfa-2a (Pegasys) was evaluated in multiple phase 3, randomized clinical trials, as monotherapy and in combination with lamivudine, for patients with HBV infection. All subjects were adults with compensated liver disease, had chronic HBV infection and evidence of HBV replication (serum HBV greater than 500,000 copies/mL for HBeAg-positive patients and greater than 100,000 copies/mL for HBeAg-negative patients). All subjects had serum ALT between 1 and 10 times the upper limit of normal (ULN). Treatment with peginterferon alfa-2a (Pegasys) exhibited significant serological, virological, and histological responses at the treatment interval of 24 weeks. Co-administration of lamivudine with Pegasys did not result in additional sustained response as compared to Pegasys monotherapy.

VII. In the setting of chronic hepatitis C (HCV), the sustained virological response (SVR) is defined as undetectable HCV RNA in 12 weeks (SVR 12) or 24 weeks (SVR 24) after treatment completion.

Cure rate, which achieves SVR, is more than 99%. SVR is generally associated with resolution of liver disease in patient without cirrhosis, but in the patient with cirrhosis there remains risk of life-threatening complications.

VIII. Ppeginterferon alfa-2a (Pegasys) has been studied as monotherapy and in combination with ribavirin in seven randomized, active-controlled clinical trials. Pooled population analysis showed the participants in these trials had HCV genotype 1 through 6, were of ages 5 years and above, and had detectable viral load at treatment initiation. Therapeutic responses were observed at median 12 weeks of treatment and durability of response sustained up to the 48-week trial window. Recommended total duration of therapy for peginterferon alfa-2a (Pegasys) is up to 48 weeks (per FDA-approval).

IX. The only guideline recommended treatment of chronic hepatitis D is interferon alfa (IFN-a). Peginterferon alfa is the drug of choice without clear differences in efficacy between peginterferon alfa-2a (Pegasys) or peginterferon alfa-2b (Pegintron). Treatment success, defined as undetectable HDV RNA at 24 weeks after completing treatment, ranges from 23% to 57%. Late relapses can occur with longer follow-up, leading to very low rates of sustained HDV-RNA undetectability. In the multicenter HIDIT-1 (Hep-Net-International-Delta-Hepatitis-Intervention-Study 1) study of peginterferon alfa-2a (Pegasys) for 48 weeks with or without adefovir, 40% of patients achieved an undetectable HDV-RNA level 24 weeks after completing therapy, but at a mean follow-up 4.3 years later, only 12% remained undetectable.

X. Although not FDA-approved, use of peginterferon alfa-2a (Pegasys) is supported by NCCN guidelines (category 2A recommendation) for the treatment of essential thrombocythemia (ET) and polycythemia vera (PV). PV and ET are BCR-ABL1–negative myeloproliferative neoplasms. Both diseases are characterized by a clonal myeloid proliferation with excessive production of blood elements. The hallmarks of ET and PV include an increased risk of thrombohemorrhagic complications, and a variable risk of transformation to myelofibrosis (MF) and/or acute myeloid leukemia (AML). Recommended use of peginterferon alfa-2a (Pegasys) in these settings is based on multiple clinical trials and retrospective studies. Notably, a phase 2 open-label clinical trial assessed Pegasys for induction of complete (CR) and partial (PR) hematologic responses in patients with high-risk ET (n=65) or PV (n=50), who were either refractory or intolerant to HU. The overall response rates (ORRs; CR/PR) at 12 months were 69.2% (43.1% and 26.2%) in ET patients and 60% (22% and 38%) in PV patients. This clinical trial was further extended to a confirmatory phase 3 trial using hydroxyurea as active comparator (N=168), wherein similar ORR was observed in the treatment arm. The treatment efficacy was comparable to hydroxyurea.

XI. For PV and ET patient populations, high-risk disease is defined by a history of thrombosis, age >60 years, a history of bleeding (ET only), platelet counts >1500 X 10^9/L in ET and >1000 X 10^9/L in PV, vasomotor symptoms (erythromelalgia, severe migraine headaches), significant or symptomatic splenomegaly, and the presence of diabetes or uncontrolled hypertension. However, younger patients (<60 years) without any other defining factors may qualify for cytoreductive therapy with peginterferon alfa-2a (Pegasys) when hydroxyurea is contraindicated (e.g. during pregnancy).

XII. There is lack of efficacy and safety data for use of peginterferon alfa-2a (Pegasys) in pediatric population with ET and/ or PV.

Investigational or Not Medically Necessary Uses

I. Peginterferon alfa-2a (Pegasys) has been investigated for safety and efficacy in some the following indications. Safety and efficacy have not been established in all of the following:

A. Chronic hepatitis C: Although included as an FDA-approved use in the manufacturer's prescribing information for the treatment of chronic hepatitis C (HCV) infection in compensated liver disease, the WHO and AALSD guidelines no longer recommend interferon-based regimens for HCV infection. Recently updated 2019 AASLD guidelines for treatment of hepatitis C recommend use of newer direct antiviral agents (DAA) as preferred treatment regimens. Overall, it is guideline consensus that peginterferon alfa-2a based treatments have relatively lower efficacy, longer onset of action and higher safety concerns. Therefore, use of peginterferon alfa-2a is recommended for limited situations when all DAA are contraindicated.

B. Myelofibrosis: NCCN guideline for myeloproliferative neoplasms recommends use of peginterferon alfa-2a (Pegasys) as 'useful in certain circumstances' as a possible alternative to ruxolitinib (Jakafi) and hydroxyurea, only when cytoreduction is considered symptomatically beneficial. This recommendation stems from a retrospective case study and observational single-center open-label trial in 30 patients, wherein 7% CR and 30% PR were reported. Overall quality of evidence is considered low.

C. Systemic mastocytosis: peginterferon alfa-2a (Pegasys) was included in NCCN guidelines for systemic mastocytosis (SM) (category 2A recommendation) as a possible treatment option for advanced SM patients. This recommendation is restricted to patients with slowly progressing disease without need for rapid cytoreduction. Tyrosine kinase inhibitors (TKI), midostaurine (Rydapt), and cladribine remain preferred therapeutic options in this space. Guidelines note that alfa interferon has recently fallen out of favor because of its slow onset of action and poor tolerability. Given the potential harmful effects of kinase inhibitors on germ cells and cladribine on the fetus (both pregnancy category D), alfa interferon may be an option in pregnancy. However, there are no supporting clinical trials to establish the efficacy and safety of peginterferon alfa-2a (Pegasys) in this patient population.

D. Chronic myelogenous leukemia (CML): NCCN guidelines recommend use of interferon alfa for management of CML during pregnancy due to contraindication to use of tyrosine kinase inhibitors (TKI) and hydroxyurea in this population. It is noted that if introduced earlier (during 1st trimester), the use of interferon may preserve molecular remission after discontinuation of TKI or HU. However, data are insufficient to establish the use of peginterferon alfa-2a (Pegasys) in pregnancy.

E. Renal cell carcinoma (RCC): interferon-alfa was studied in RCC as an adjuvant therapy for high-risk, clear cell, localized RCC post nephrectomy. Randomized trials in patients who had locally advanced, completely resected RCC showed no delay in time to relapse or improvement in survival with adjuvant therapy.

F. Malignant melanoma: Interferon alfa-2b (Intron A) and peginterferon alfa-2b (Sylatron) have supporting clinical evidence and are FDA-approved for malignant melanoma. Safety and efficacy of peginterferon alfa-2a (Pegasys) has not been established in these settings.

G. Hairy cell leukemia: NCCN guidelines for hairy cell leukemia recommend peginterferon alfa-2a as a possible alternative for the treatment of relapsed/ refractory hairy cell leukemia. However, purine analogs (cladribine, pentostatin) and rituximab remain preferred

therapeutic options in this space. In a 1995 phase III intergroup study (N=319), efficacy and safety of pentostatin was compared with that of interferon alfa with a treatment follow-up of median 57 months. Subjects receiving Pentostatin reported higher complete remission (CR) rates versus those with interferon alfa treatment (76% vs 11%; p< 0.0001) along with longer relapse-free survival (RFS) (not reached vs 20 months; p< 0.0001). NCCN guidelines note that with the advent of purine analogs, the role of interferon alfa as a treatment option for hairy cell leukemia is limited.

References

1. Pegasys (peginterferon alfa-2a) [prescribing information]. South San Francisco, CA: Genentech Inc; October 2020.
2. Abbas Z, Memon MS, Mithani H, Jafri W, Hamid S. Treatment of chronic hepatitis D patients with pegylated interferon: a real-world experience. Antivir Ther. 2014;19(5):463-8.
3. Hepatitis C Guidance 2018 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection; https://www.aasld.org/publications/practice-guidelines
4. Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance; 2018, hematology; 67 (4), 1560. https://www.aasld.org/publications/practice-guidelines.
5. World Health Organization Guidelines For The Care And Treatment of Persons Diagnosed With Chronic Hepatitis C Virus Infection. 2018; https://apps.who.int/iris/bitstream/handle/10665/273174/9789241550345-eng.pdf?ua=1
6. Yacoub A, Mascarenhas J, et al.; Pegylated interferon alfa-2a for polycythemia vera or essential thrombocythemia resistant or intolerant to hydroxyurea. Blood. 2019 Oct 31;134(18):1498-1509.
7. U.S. National Library of Medicine; Clinical Trials database; NCT01259856; NCT00452023; NCT00241241; https://clinicaltrials.gov.
8. Heidrich B, Yurdaydın C, Kabaçam G, Ratsch BA, Zachou K, Bremer B, Dalekos GN, Erhardt A, Tabak F, Yalcin K, Gürel S, Zeuzem S, Cornberg M, Bock CT, Manns MP, Wedemeyer H; HIDIT-1 Study Group. Late HDV RNA relapse after peginterferon alpha-based therapy of chronic hepatitis delta. Hepatology. 2014 Jul;60(1):87-97.

Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria update: Transition from criteria to policy format and review of FDA-approved and guideline supported indications for peginterferon alfa-2a (Pegasys). Added supporting evidence for all indications listed in the policy. Removed indication of chronic hepatitis C per current AALSD and WHO guideline recommendation. Reviewed available evidence for indications listed under not medically necessary and investigational uses and added relevant clinical information to supporting evidence section	12/2020
Previous reviews and updates	12/2012; 08/2012; 12/2011; 12/2008; 11/2007
Criteria created	01/2006

Policy Type: PA/SP Pharmacy Coverage Policy: UMP149

Description

Pegvisomant (Somavert) selectively binds to growth hormone (GH) receptors on cell surfaces, where it blocks the binding of endogenous GH, and thus interferes with signal transduction. Inhibition of GH action results in decreased serum concentrations of insulin-like growth factor-I (IGF-I), as well as other GH-responsive serum proteins, including IGF binding protein-3 (IGFBP-3), and the acid-labile subunit (ALS).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
pegvisomant (Somavert)	10 mg vial	Acromegaly	60 vials/30 days
	15 mg vial		60 vials/30 days
	20 mg vial		30 vials/30 days
	25 mg vial		30 vials/30 days
	30 mg vial		30 vials/30 days

Initial Evaluation

I. Pegvisomant (Somavert) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an endocrinologist; **AND**
   C. A diagnosis of **acromegaly** when the following are met:
      1. Diagnosis is confirmed by elevated serum IGF-1 for member's age and gender, (including laboratory reference range); **OR**
         a. If normal IGF-1, elevated growth hormone level nadir of > 1 ng/mL during an oral glucose tolerance test (OGTT); **AND**
      2. Documentation of inadequate response to surgery or radiation therapy; **AND**
      3. Treatment with octreotide (Sandostatin), cabergoline, or bromocriptine (Parlodel) has been ineffective, contraindicated, or not tolerated

II. Pegvisomant (Somavert) is considered <u>investigational</u> when used for all other conditions.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (improvements in sleep apnea, tissue swelling, headache, arthralgias); **AND**
IV. Serum IGF-1 level has decreased from baseline or normalized (according to the lab reference range based on member age and gender)

Supporting Evidence

I. Acromegaly is a hormonal disorder that occurs when the pituitary gland produces too much growth hormone (GH). Typically, this is caused by adenomas (benign tumor) on the pituitary gland. Diagnosis typically occurs in middle-aged adults; however, symptoms can appear at any age. Surgical intervention is the preferred treatment.
II. According to the American Association of Clinical Endocrinologists (AACE) guidelines, medical therapy is pursued in patients with a tumor that cannot be completely removed surgically, have no compressive tumor effects, are poor surgical candidates, or prefer medical management. Goals of therapy include the normalization of biochemical variables, reversal of mass-effects of the tumor, improvement in signs, symptoms, and comorbidities of disease, and the minimization of long-term mortality risk. In most patients, medical therapy is used as adjuvant treatment in the setting of persistent disease despite surgical intervention.
III. AACE guidelines recommend a random IGF-1 value (a marker of integrated GH secretion) to be measured for diagnosis and as post-intervention therapeutic monitoring. A serum IGF-1 level should be remeasured at 12 weeks; a normal IGF-1 value is consistent with surgical remission. If a repeat serum IGF-1 value is reduced from baseline, but is still elevated at 12 weeks, an additional repeat testing is done in another 9 to 12 weeks to determine the presence of delayed biochemical normalization, before proceeding with potential surgical re-exploration, medical therapy, or radiation therapy. Additionally, an oral glucose tolerance test is also utilized as a diagnostic tool, especially in conditions that are associated with lower IGF-1 concentrations (e.g., hypothyroidism, malnutrition, uncontrolled type 1 diabetes, liver failure, renal failure, oral estrogen use) where the diagnosis of acromegaly could be missed. Inability to suppress serum GH to less than 1 ng/mL after glucose administration is considered the diagnostic criterion for acromegaly and is the gold standard for determining control of GH secretion after surgical treatment.
IV. Per guidelines, there are three classes of medical therapy: dopamine agonists (e.g. caberfoline, bromocriptine), somatostatin analogues (e.g. octreotide, lanreotide), and a GH-receptor antagonist (e.g. pegvisomant). Dopamine agonists are considered first-line medical therapy as they are relatively inexpensive in comparison to alternative medical therapy options and have simple oral administration.
V. With the administration of pegvisomant (Somavert), serum IGF-1 should be measured alone to monitor the dose efficacy. There is no benefit from the measurement of serum GH in

conjunction with pegvisomant (Somavert) therapy. GH levels increase when pegvisomant (Somavert) is administered, and the GH levels have no effect on pegvisomant (Somavert) dosing.

Investigational or Not Medically Necessary Uses

I. There is limited to no evidence to support the use of pegvisomant (Somavert) in any other condition.

References

1. Somavert [Prescribing Information]. New York, NY: Pfizer; September 2019.
2. UpToDate, Inc. Treatment of acromegaly. UpToDate [database online]. Waltham, MA. Last updated August 20, 2019 Available at: http://www.uptodate.com/home/index.html.
3. UpToDate, Inc. Diagnosis of acromegaly. UpToDate [database online]. Waltham, MA. Last updated August 26, 2019 Available at: http://www.uptodate.com/home/index.html.
4. Katznelson L, Atkinson JL, Cook DM, et al. American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly--2011 update. Endocr Pract. 2011 Jul-Aug;17(Suppl 4):1-44.

Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of confirmed diagnosis requirements (elevated IGF-1 o**r** GH level). Added requirement of reduced or normalized IGF-1 levels at renewal. Updated initial approval duration from 12 months to 6 months.	05/2020
Addition of renewal criteria. Added age requirement of 18 years or older. Added requirement for agent to be prescribed by or in consultation with an endocrinologist.	12/2019
Policy created	01/2006

Policy Type: PA/SP Pharmacy Coverage Policy: UMP191

Split Fill Management*

Description

Pemigatinib (Pemazyre) is an orally administered fibroblast growth factor receptor (FGFR) inhibitor, with activity against FGFR1 and FGFR2 fusions or rearrangements.

Length of Authorization

- N/A

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
pemigatinib (Pemazyre)	13.5 mg tablet	Previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma in adults with FGFR2 fusions or rearrangements	14 tablets/21 days
	9 mg tablet		
	4.5 mg tablet	Relapsed or refractory myeloid/lymphoid neoplasms (MLNs) with FGFR1 rearrangement.	30 tablets/30 days

Initial Evaluation

I. **Pemigatinib (Pemazyre)** is considered investigational when used for all conditions, including but not limited to cholangiocarcinoma and relapsed or refractory myeloid/lymphoid neoplasms (MLNs).

Renewal Evaluation

I. N/A

Supporting Evidence

Treatment of Cholangiocarcinoma

I. Pemigatinib (Pemazyre) is the first targeted therapy for cholangiocarcinoma that harbors FGFR2 fusions or rearrangements. Pemigatinib (Pemazyre) is a second-line chemotherapy option. Guideline preferred first line chemotherapy is gemcitabine and cisplatin, while second-line options include mFOLFOX, FOLFIRI, and regorafenib (Stivarga).

II. Pemigatinib (Pemazyre) was evaluated in FIGHT-202, an open-label, single-arm, multi-cohort Phase 2 trial. Patients (N=146) with locally advanced or metastatic CCA, previously treated with at least 1 chemotherapy were included. FDA approval was based on the overall response rate (ORR) in patients with FGFR2 gene fusion or rearrangements.

III. The primary efficacy endpoint was objective response rate (ORR). Secondary endpoints were progression-free survival (PFS), overall survival (OS), and duration of response (DOR). Based on analysis of this clinical trial data, quality of the evidence is considered low given the lack of comparator and open-label trial design, as well as, the lack of clinically meaningful outcomes in morbidity, mortality, and quality of life – medication efficacy has not yet been confirmed.

IV. Pemigatinib (Pemazyre) received accelerated approval from the FDA based on ORR and DOR. Continued approval for this drug may be contingent upon verification of clinical benefit in confirmatory trials. There is a Phase 3 trial underway to assess pemigatinib (Pemazyre) monotherapy versus gemcitabine + cisplatin in the first-line treatment of CCA with FGFR2 alterations.

V. The safety profile of pemigatinib (Pemazyre) was based on adverse reactions observed in all cohorts during CT (N=146). The most common adverse events (≥20% incidence) included hyperphosphatemia, alopecia, nausea, diarrhea, nail toxicity, back pain, fatigue, dysgeusia, dry eyes, and serous retinal detachment. There are no specific contraindications to pemigatinib (Pemazyre); however, warnings and precautions include: ocular toxicity, hyperphosphatemia, GI toxicity and renal function. Pemigatinib (Pemazyre) showed 9% treatment discontinuation rate, 14% dose reductions rate, and 42% dose interruption rate due to adverse events.

VI. As of January 2023, The National Comprehensive Cancer Network (NCCN) treatment guideline for hepatobiliary cancer has included pemigatinib (Pemazyre) as second-line treatment with a Category 2A recommendation. Pemigatinib (Pemazyre) is useful in treatment of tumor with confirmed FGFR2 fusions or rearrangements, and which are refractory to first line chemotherapy.

Treatment of Myeloid/Lymphoid Neoplasms

VII. Myeloid/lymphoid neoplasms (MLNs) with FGFR1 rearrangement are rare hematologic malignancies included in the World Health Organization (WHO) major category "MLNs with eosinophilia and rearrangements of PDGFRA, PDGFRB, FGFR1, or with PCM1-JAK2." In this group of neoplasms the formation of a fusion gene, or (rarely) from a mutation, results in the expression of an aberrant tyrosine kinase. MLNs with FGFR1 rearrangement are an extremely rare and aggressive that impacts less than 1 in 100,000 people in the United States per year with less than 100 patients reported worldwide as of 2010.

VIII. In August 2022, pemigatinib (Pemazyre) was approved for adults with relapsed or refractory myeloid/lymphoid neoplasms (MLNs) with fibroblast growth factor receptor 1 (FGFR1) rearrangement. Approval was based on interim results from the Phase 2 FIGHT-203 trial. FIGHT-203 was a multicenter, open-label, single-arm trial including patients with relapsed or refractory MLNs with FGFR1 rearrangement.

IX. Adult participants (N=28) who were not candidates for stem cell transplantation or other disease modifying therapy along with confirmed MLN with 8p11 rearrangement known to lead FGFR1 activation were included in the study population. The primary outcome measure was complete response (CR) rate and was reported per the morphologic disease type. Of the 18 patients with chronic phase in the marrow with or without extramedullary disease (EMD), 14 achieved CR (78%; 95% CI: 52, 94). The median time-to-CR was 104 days (range, 44 to 435). The median duration was not reached (range: 1+ to 988+ days). Of the 4 patients with blast phase in the marrow with or without EMD, 2 achieved CR (duration: 1+ and 94 days). Of 3 patients with EMD only, 1 achieved

a CR (duration: 64+ days). Secondary endpoints reported in the interim results included complete cytogenic response (CCyR). In all 28 patients (including 3 patients without evidence of morphologic disease), the CCyR rate was 79% (22/28; 95% CI: 59, 92). Progression free survival and overall survival are to be reported at trial conclusion.

X. The safety profile of pemigatinib (Pemazyre) was based on 34 patients. All patients experienced ≥ 1 treatment-emergent adverse event (TEAE). The most common any-grade hematologic TEAEs were anemia (35%), thrombocytopenia (12%), and neutropenia (3%). The most common nonhematologic TEAEs (any grade) were hyperphosphatemia (68%), alopecia (59%), and diarrhea (50%). Grade 3 and 4 TEAEs occurred in 85% of patients. Reported TEAEs led to treatment interruption in 65% of patients, dose reduction in 59% of patients, and discontinuation in 12% of patients.

XI. Based on the interim results posted trial does not offer OS or PFS data. Overall survival and progression free survival data is to be reported as the conclusion of the phase 2 trial. Interim results without OS data limit the applicability of this treatment outside of a clinical trial space. Current NCCN guidelines prefer to clinical trial, and now pemigatinib (Pemazyre), as first line. However, there is a caveat in the guidelines that early referral to allogeneic HCT should be considered for eligible patients, since TKI therapy alone does not result in durable remissions. Given the lack of durability in TKI monotherapy, including pemigatinib (Pemazyre), the level of evidence is considered low.

XII. An FDA-approved test for detection of FGFR1 rearrangement in patients with relapsed or refractory myeloid/lymphoid neoplasm for selecting patients for treatment with pemigatinib (Pemazyre) is not available. However, FGFR 1 rearrangement can be detected with an 8p11 translocation on conventional cytogenetics and/or on break-apart fluorescence in situ hybridization testing (FISH).

Investigational or Not Medically Necessary Uses

I. Pemigatinib (Pemazyre) has not been sufficiently studied for safety and efficacy for conditions other than cholangiocarcinoma and myeloid/lymphoid neoplasms to date.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Krasinskas A, Pawlik TM, et al. Distal bile duct. In: AJCC Cancer Staging Manual, 8th, Amin MB. (Ed), AJCC, Chicago 2017. p.317.
2. Aloia T, Pawlik TM, et al. Intrahepatic bile ducts. In: AJCC Cancer Staging Manual, 8th, Amin MB (Ed), AJCC, Chicago 2017. p.295.
3. Razumilava, N; Gores, GJ. "Cholangiocarcinoma". Lancet. 2014, 383, (9935): 68–79.
4. Patel N; Benipal B. 2019, Incidence of Cholangiocarcinoma in the USA from 2001 to 2015: A US Cancer Statistics Analysis of 50 States. Cureus. 2019;11(1): e3962.

5. Valle J, Wasan H, et al. Cisplatin plus gemcitabine vs gemcitabine for biliary tract cancer. N. Engl. J. Med. 2010; 362(14): 1273-81.
6. Blechacz B. Cholangiocarcinoma: Current Knowledge and New Developments. Gut Liver 2017; 11(1):13-26.
7. Nakamura H, Arai Y, Totoki Y, et al. Genomic spectra of biliary tract cancer. Nature Genetics 2015; 47: 1003-10.
8. Krook MA, Lenyo A, Wilberding M, et al. Efficacy of FGFR inhibitors and combination therapies for acquired resistance in FGFR2-fusion cholangiocarcinoma. Molecular Cancer Therapeutics 2020; 19: 847-57.
9. National Comprehensive Cancer Network. Hepatobiliary Cancers (Version 3.2022). NCCN. October 14, 2022. Accessed October 26, 2022. hepatobiliary.pdf (nccn.org)
10. Abou-alfa GK et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicenter, open-label, phase 2 study. Lancet Oncol. 2020 May;21(5):671-684. (NCT02924376)
11. A study to evaluate the efficacy and safety of pemigatinib versus chemotherapy in unresectable or metastatic cholangiocarcinoma (FIGHT-302), clinicaltrials.gov; NCT03656536. https://clinicaltrials.gov/ct2/show/NCT03556536.
12. National Comprehensive Cancer Network. Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes (Version 2.2022). NCCN. October 18, 2022. Accessed October 26, 2022.
13. Pemazyre. Package insert. Incyte Corporation; 2022.
14. Pemazyre (pemigatinib) product dossier. Incyte Corporation. September 14, 2022.
15. Gotlib J, Kiladjian JJ, Vannucchi A, et al. A Phase 2 Study of Pemigatinib (FIGHT-203; INCB054828) in Patients with Myeloid/Lymphoid Neoplasms (MLNs) with Fibroblast Growth Factor Receptor 1 (FGFR1) Rearrangement (MLN FGFR1). *Blood*. 2021; 138 (Supplement 1): 385. doi: https://doi.org/10.1182/blood-2021-148103

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy

Policy Name	Disease state
erdafitinib (Balversa™)	Advanced or metastatic urothelial carcinoma FGFR3 or FGFR2 genetic alteration, second-line after platinum therapy progression
infigratinib (Truseltiq™)	Previously treated adults with unresectable, locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangement
Multi-Targeted Tyrosine Kinase Inhibitors (Multi-TKI)	Unresectable Hepatocellular Carcinoma
	Advanced Renal Cell Carcinoma
	Recurrent, High-risk or Metastatic Endometrial Carcinoma
	Locally Recurrent or Metastatic Progressive Thyroid Cancer
	Unresectable Liver Carcinoma
midostaurin (Rydapt®)	Acute myeloid leukemia, newly diagnosed, FLT3 mutation-positive, in combination with cytarabine/daunorubicin induction and cytarabine consolidation
ponatinib (Iclusig®)	CP-CML with resistance or intolerance to two prior kinase inhibitors
	AP-CML, BP-CML, and Ph+ ALL for whom no other kinase inhibitors are indicated
	T315I-positive CML (any phase) or T315I-positive Ph+ ALL

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated policy to include relapsed/ refractory MLNs with supporting evidence. Added SF criteria, updated references formatting, included related policies table.	01/2023
Policy created	06/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP085

Split Fill Management*

Description

Pexidartinib (Turalio) is an oral kinase inhibitor FDA-approved 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.

Length of Authorization

- Initial: Six months, split fill for the first three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
pexidartinib (Turalio)	125 mg capsule	Tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery	120 capsules/30 days

Initial Evaluation

I. **Pexidartinib (Turalio)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. The medication is prescribed by, or in consultation with, an oncologist or orthopedic surgeon; **AND**
   C. Member has a confirmed diagnosis of **symptomatic tenosynovial giant cell tumor; AND**
   D. A surgical/orthopedic oncologist or orthopedic surgeon has evaluated that the member is not a candidate for surgery; **AND**
   E. Member does not have preexisting increased serum transaminases such as ALT and AST or an indication of hepatotoxicity; **AND**
   F. The medication is used as a monotherapy

II. Pexidartinib (Turalio) is considered investigational when used for all other conditions, including but not limited to:
   A. Metastatic tenosynovial giant cell tumor (TGCT)
   B. Active cancer that requires therapy (e.g. surgical, chemotherapy, or radiation therapy)

C. Pexidartinib (Turalio) is used in combination with other tyrosine kinase inhibitors that also target colony-stimulating factor (CSF1) or the CSF1 receptor (CSF1R) (e.g., imatinib, nilotinib, sorafenib, or sunitinib)

Renewal Evaluation

A. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
B. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
C. Member has an absence of unacceptable toxicity from the medication; **AND**
D. Clinical documentation showing symptomatic/disease improvement(s) including
    1. Stable or improved range of motion of affected joint; **OR**
    2. Stable or improved pain in affected joint; **OR**
    3. Stable or improved in stiffness of affected joint

Supporting Evidence

I. Pexidartinib (Turalio) is FDA-approved 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.
II. Tenosynovial giant cell tumor is also referred to as giant cell tumor of the tendon sheath (GCTTS) or pigmented villonodular synovitis (PVNS).
III. Patients with recurrent and/or relapsed TGCT may typically undergo surgical interventions, however, if further surgery would result in significant morbidity or functional impairment, systemic therapy such as pexidartinib (Turalio) may be beneficial.
IV. Pexidartinib (Turalio) was studied in a clinical trial with two parts:
    - Part 1: A randomized, double-blind, multicenter, Phase 3 study (n=120) patients with symptomatic advanced TGCT for whom surgical removal of the tumor would be associated with potentially worsening functional limitation or severe morbidity. The primary efficacy outcome in Part 1 was overall response rate (ORR): 39% (24 of 61) with pexidartinib (Turalio) vs. 0% with placebo at week 25 (p<0.0001); 53% at data cutoff.
    - Part 2: An open-label, Phase 3 trial for patients (n=78; 30 from the placebo group) who completed the part 1, evaluating ORR of the patients on the crossover treatment. The primary efficacy outcome in Part 2 was ORR: 30% (9 of 30) at week 25; 53% (16 of 30) at data cutoff.
V. Pexidartinib (Turalio) has boxed warnings and REMS program for the risk of serious and potentially fatal liver injury and embryo-fetal toxicity.
VI. Common adverse events (>20%) in the clinical trial were: hair color change (67%), fatigue (54%), AST increase (39%), nausea (38%), ALT increase (28%), and dysgeusia (25%).
VII. Most common grade 3 or 4 adverse events occurring at a higher incidence in patients treated with pexidartinib (Turalio) were increases in liver enzymes. Hepatic adverse events were also the

most common cause of treatment interruption, dose reduction (38% combined), or treatment discontinuation (13%) in the pexidartinib (Turalio) group.

VIII. In the clinical trial (ENLIVEN), pexidartinib (Turalio) was used as a single-agent therapy.

Investigational or Not Medically Necessary Uses

I. All condition(s) listed as investigational use
   A. These conditions are parts of the exclusion criteria from the ENLIVEN clinical trial. Safety and efficacy of pexidartinib (Turalio) for these conditions are not studied and unknown.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Turalio [Prescribing Information]. Daiichi Sankyo, Inc. Basking Ridge, NJ. August 2019.
2. Tap WD, Gelderblom H, Palmerini E, et al. Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial. *Lancet*. 2019;394(10197):478-487. doi: 10.1016/S0140-6736(19)30764-0.
3. UpToDate, Inc. Treatment for tenosynovial giant cell tumor and other benign neoplasms affecting soft tissue and bone. UpToDate [database online]. Waltham, MA. Updated September 4, 2019. Available at: http://www.uptodate.com/home/index.html. Accessed September 10, 2019.
4. Scharschmidt, T. (2017). Tenosynovial Giant Cell Tumor - NORD (National Organization for Rare Disorders). [online] NORD (National Organization for Rare Disorders). Available at: https://rarediseases.org/rare-diseases/tenosynovial-giant-cell-tumor. Accessed 30 Sep. 2019.
5. National Comprehensive Cancer Network. NCCN Guidelines: Soft Tissue Sarcoma. Available at: https://www.nccn.org/professionals/physician_gls/pdf/sarcoma_blocks.pdf. Updated August 16, 2019. Accessed September 3, 2019.
6. Cassier PA, Gelderblom H, Stacchiotti S, et al. Efficacy of imatinib mesylate for the treatment of locally advanced and/or metastatic tenosynovial giant cell tumor/pigmented villonodular synovitis. *Cancer*. 2012;118(6):1649-55. doi: 10.1002/cncr.26409.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated to include 125mg tablet as the 200mg is discontinued; Updated renewal wording to include standard formatting; updated minor formatting things	01/2023
Policy created	09/2019
Previous reviews	09/2019; 11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP148

Description
Pegvaliase (Palynziq) is a PEGylated phenylalanine-metabolizing enzyme that works to reduce blood phenylalanine concentrations by converting phenylalanine to ammonia and transcinnamic acid.

Sapropterin dihydrochloride (Kuvan) is a synthetic form of the cofactor BH4 (tetrahydrobiopterin) for the enzyme phenylalanine hydroxylase (PAH). PAH hydroxylates phenylalanine to form tyrosine. BH4 activates residual PAH enzyme, improving normal phenylalanine metabolism and decreasing phenylalanine levels.

Length of Authorization
- Initial:
  - Pegvaliase (Palynziq): Six months
  - Sapropterin dihydrochloride (Kuvan): Two months
- Renewal:
  - Pegvaliase (Palynziq): 12 months
  - Sapropterin dihydrochloride (Kuvan): 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
pegvaliase (Palynziq)	Phenylketonuria (PKU)	2.5 mg/0.5 mL	8 syringes/30 days
		10 mg/0.5 mL	30 syringes/30 days
		20 mg/1 mL	90 syringes/30 days
sapropterin dihydrochloride (generic Kuvan)		100 mg tablets	20 mg/kg/day
		100 mg powder for oral solution	
		500 mg powder for oral solution	
sapropterin dihydrochloride (Kuvan)		100 mg tablets	20 mg/kg/day
		100 mg powder for oral solution	
		500 mg powder for oral solution	
sapropterin dihydrochloride (Javygtor)		100 mg tablets	20 mg/kg/day
		100 mg powder for oral solution	
		500 mg powder for oral solution	

Initial Evaluation
I. **Pegvaliase (Palynziq), sapropterin dihydrochloride (Kuvan), and sapropterin dihydrochloride (Javygtor)** may be considered medically necessary when the following criteria below are met:

A. Medication is prescribed by, or in consultation with, a metabolic diseases specialist or a provider who specializes in the treatment of phenylketonuria and other metabolic disorders; **AND**
B. Documentation of current blood phenylalanine concentration is submitted; **AND**
C. Documentation noting member compliance with a phenylalanine restricted diet; **AND**
D. Member is going to continue to restrict phenylalanine from their diet; **AND**
E. A diagnosis of **phenylketonuria (PKU)** when the following are met:
    1. Request is for **generic sapropterin dihydrochloride**; **AND**
        i. Member has uncontrolled blood phenylalanine concentrations greater than 360 micromol/L on existing management [e.g., phenylalanine restricted diet]; **AND**
        ii. Not used in combination with pegvaliase (Palynziq); **OR**
    2. Request is for **pegvaliase (Palynziq)**; **AND**
        i. Member is 18 years of age or older; **AND**
        ii. Member has uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management [e.g., phenylalanine restricted diet, Kuvan (sapropterin)]; **AND**
        iii. Not used in combination with sapropterin dihydrochloride (Kuvan); **OR**
    3. Request is for **dihydrochloride (Kuvan) or sapropterin dihydrochloride (Javygtor)**; **AND**
        i. Member has tetrahydrobiopterin- (BH4-) responsive PKU; **AND**
        ii. Member has uncontrolled blood phenylalanine concentrations greater than 360 micromol/L on existing management [e.g., phenylalanine restricted diet]; **AND**
        iii. Treatment with generic sapropterin dihydrochloride (generic for Kuvan) has been ineffective, contraindicated, or not tolerated; **AND**
        iv. Not used in combination with pegvaliase (Palynziq).

II. Pegvaliase (Palynziq) and sapropterin dihydrochloride (Kuvan) is considered investigational when used for all other conditions, including but not limited to:
    A. Liver Cirrhosis and Portal Hypertension
    B. Autism spectrum disorder
    C. Gastroparesis
    D. Schizophrenia

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Attestation noting member compliance with a phenylalanine restricted diet; **AND**
IV. Documentation of current blood phenylalanine concentration is submitted; **AND**

V. Attestation of member compliance to therapy with pegvaliase (Palynziq) or sapropterin dihydrochloride (Kuvan; Javygtor); **AND**

VI. Member had a response to pegvaliase (Palynziq) therapy defined as:
   A. At least a 20% reduction in blood phenylalanine levels from baseline; **OR**
   B. Blood phenylalanine concentration less than or equal to 600 micromol/L; **OR**

VII. Member had a response to generic sapropterin dihydrochloride or sapropterin dihydrochloride (Kuvan; Javygtor) therapy defined as:
   A. At least a 30% reduction in in blood phenylalanine levels from baseline; **OR**
   B. Clinical response (e.g., cognitive and/or behavioral improvements)

Supporting Evidence

I. Phenylketonuria (PKU) is an inherited disorder that increases the levels of a substance called phenylalanine in the blood. If PKU is not treated, phenylalanine can build up to harmful levels in the body causing intellectual disability and other serious health problems. Seizures, delayed development, behavioral problems, and psychiatric disorders are also common. Considering all the aspects of this disease state and that it is crucial to identify if a member is responding to therapy, the medication needs to be prescribed by, or in consultation with, a metabolic diseases specialist or a provider who specializes in the treatment of phenylketonuria and other metabolic disorders.

II. It is crucial for treatment and prevention of disease progression to obtain the blood levels of phenylalanine (PHE) prior to treatment start.

III. According to the American College of Medical Genetics and Genomics (ACMG) Practice Guidelines, dietary therapy, with restriction of dietary phenylalanine intake, remains the mainstay of therapy for PAH deficiency. The goal of the diet is to provide enough natural protein for the patient to be healthy and grow normally with sufficient restriction to keep blood phenylalanine in the treatment range. PKU medication is not a replacement for diet.

IV. Pegvaliase (Palynziq) is FDA approved to reduce blood phenylalanine concentrations in adult patients with PKU who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management [e.g., phenylalanine restricted diet, Kuvan (sapropterin)].

V. The safety and efficacy of pegvaliase (Palynziq) in pediatric patients has not been assessed in clinical trials and therefore there is no robust evidence to support the use. However, pegvaliase (Palynziq) has been approved in the European Union for patients aged 16 years or older with a dose regimen that mirrors adult dosing. Additionally, three open label phase 2 studies evaluating use of Palynziq in patients aged 16 years or older have been completed in the U.S. (NCT01560286, NCT00925054, NCT00924703) which show some signals of efficacy. However, studies have a small sample size, low enrollment of patients less than 18 years old, and possible safety concerns, thus true safety and efficacy of Palynziq in the subset of patients aged 16 to 18 years remains unknown.

VI. There is no robust clinical trial data to show an increase benefit and the safety profile of concomitant use of pegvaliase (Palynziq) and sapropterin dihydrochloride (Kuvan).

VII. ACMG guidelines note that approximately 25–50% of the patients with PAH deficiency are sapropterin-responsive. Patients with mild PAH deficiency are most likely to respond because some stable protein is required for sapropterin to function; nonetheless, responsive patients are

identified even among those with complete PAH deficiency. Genotype may be predictive of sapropterin response, but genotype-phenotype correlations thus far are imperfect. Therefore, every PAH-deficient patient should be offered a trial of sapropterin therapy to assess responsiveness. Clinical judgment is required to determine what constitutes a significant or beneficial decline in an individual patient, but 30% is often cited in the literature as evidence of effective PHE reduction. Most sapropterin responsive patients have a rapid decline in blood PHE level, but occasionally a delay of 2–4 weeks is seen. Patients with a baseline PHE level at the lower end of the treatment range (180 µmol/l or lower) rarely show a significant decline in blood PHE level, even if they are sapropterin-responsive. An improvement in neuropsychiatric symptoms or increase in PHE tolerance without a decrease in blood PHE in any patient constitutes sufficient justification to continue therapy. The blood phenylalanine concentration associated with optimal neurodevelopmental outcome is uncertain.

VIII. For sapropterin dihydrochloride (Kuvan) the response to therapy is determined by change in blood phenylalanine following treatment. If blood phenylalanine does not decrease from baseline at 10 mg/kg per day, the dose may be increased to 20 mg/kg per day. Patients whose blood phenylalanine does not decrease after 1 month of treatment at 20 mg/kg per day are non-responders and treatment should be discontinued. However, an improvement in neuropsychiatric symptoms constitutes sufficient justification to continue therapy.

IX. For pegvaliase (Palynziq) the response to therapy is determined by change in blood phenylalanine following treatment. In patients who have not achieved a response (at least a 20% reduction in blood phenylalanine concentration from pre-treatment baseline or a blood phenylalanine concentration less than or equal to 600 micromol/L) after 16 weeks of continuous treatment with the dosage of 40 mg once daily, can consider increasing to a maximum dose of 60 mg once daily. As recommended in the package insert, pegvaliase (Palynziq) should be discontinued in patients who have not achieved an adequate response after 16 weeks of continuous treatment with the maximum dosage of 60 mg once daily.

Investigational or Not Medically Necessary Uses

I. Pegvaliase (Palynziq);
   A. There is limited or no published clinical trial data to support the use of pegvaliase (Palynziq) in conditions other than PKU.

II. Sapropterin dihydrochloride (Kuvan);
   A. Liver Cirrhosis and Portal Hypertension
      i. A randomized, blinded, and placebo-controlled trial was conducted to assess the effects of sapropterin dihydrochloride (Kuvan) on hepatic and systemic hemodynamics in patients with liver cirrhosis and portal hypertension. The trial data showed that sapropterin dihydrochloride (Kuvan), did not reduce portal pressure in patients with cirrhosis.
   B. Autism spectrum disorder (ASD)
      i. A prospective 16-week open-label outpatient treatment trial of sapropterin dihydrochloride (Kuvan) for core and associated ASD symptoms in 2–6-year-old children with confirmed language and/or social delays extended the

understanding of the effect of BH_4 treatment on the cognitive and behavioral symptoms of individuals with ASD

ii. The results of a double-blind placebo-controlled crossover study, designed to examine the tetrahydrobiopterin pathway genes in autism, indicated a possible effect of BH4 treatment in children with autistic disorder, but the study does not have enough power and it wasn't designed to show efficacy and safety of the use of sapropterin dihydrochloride (Kuvan) in the treatment of autism spectrum disorder. There is no robust safety and efficacy data to support the use of sapropterin dihydrochloride (Kuvan) in patients with autism spectrum disorder.

C. Gastroparesis
   i. One small open label trial consisting of low-quality evidence. Further evaluation is needed to support the use of sapropterin dihydrochloride (Kuvan) in this setting.

D. Schizophrenia
   i. One small open label trial consisting of low-quality evidence is available with ongoing trials recruiting as of 2019. Further evaluation is needed to support use of sapropterin dihydrochloride (Kuvan) in this setting.

References

1. Palynziq [Prescribing Information]. Novato, CA: BioMarin Pharmaceutical Inc.; November 2020.
2. Kuvan [package insert]. Novato, CA: BioMarin Pharmaceutical Inc; March 2020.
3. Kuvan™ (sapropterin dihydrochloride) product dossier. BioMarin Pharmaceuticals, Inc, 2008.
4. Phenylketonuria: Screening and Management. NIH Consensus Statement Online 2000 October 16-18; 17(3): 1-27 Accessed 01/19/2009.
5. Hellekson, Karen L. Practice Guidelines: NIH ConsensusStatement on Phenylketonuria. American Family Physician. April 1, 2001.
6. Burton BK, Grange DK, Milanowski A, et al. The response of patients with phenylketonuria and elevated serum phenylalanineto treatment with oral sapropterin dihydrochloride (6R- tetrahydrobiopterin): a phase II, multicentre, open-label, screening study. J Inherit Metab Dis. 2007; 30(5):700-707.
7. Levy HL, Milanowski A, Chakrapani A, et al. Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6RBH4) for reduction ofphenylalanine concentration in patients with phenylketonuria: a phase III randomized placebo-controlled study Lancet. 2007; 370:504-510.
8. Vockley J, Andersson HC, Antshel KM, et al. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. Genet Med. 2014;16(2):188-200.
9. Reverter E, Mesonero F, Seijo S, et al. Effects of Sapropterin on Portal and Systemic Hemodynamics in Patients With Cirrhosis and Portal Hypertension: A Bicentric Double-Blind Placebo-Controlled Study. Am J Gastroenterol. 2015;110(7):985-92.
10. Frye RE, Delatorre R, Taylor HB, et al. Metabolic effects of sapropterin treatment in autism spectrum disorder: a preliminary study. Transl Psychiatry. 2013;3:e237.
11. Schnetz-boutaud NC, Anderson BM, Brown KD, et al. Examination of tetrahydrobiopterin pathway genes in autism. Genes Brain Behav. 2009;8(8):753-7.
12. Danfors T, Von knorring AL, Hartvig P, et al. Tetrahydrobiopterin in the treatment of children with autistic disorder: a double-blind placebo-controlled crossover study. J Clin Psychopharmacol. 2005;25(5):485-9.
13. ClinicalTrials.gov. Impact of KUVAN® on Gastric Relaxation in Women With Diabetic Gastroparesis. NCT01135186.
14. ClinicalTrials.gov. Kuvan in People With Schizophrenia and Schizoaffective Disorder. NCT01706965.
15. European Commission approves Palynziq® (Pegvaliase injection) for treatment of phenylketonuria (PKU) in patients aged 16 years or older. BioMarin Investors. Available at: https://investors.biomarin.com/news/news-details/2019/European-Commission-Approves-Palynziq-pegvaliase-injection-for-Treatment-of-Phenylketonuria-PKU-in-Patients-Aged-16-Years-or-Older-05-06-2019/default.aspx

16. ClinicalTrials.gov. A Study to Evaluate Subcutaneously Administered rAvPAL-PEG in Patients With Phenylketonuria for 24 Weeks. NCT01560286.
17. ClinicalTrials.gov. Dose-Finding Study to Evaluate the Safety, Efficacy, & Tolerability of Multiple Doses of rAvPAL-PEG in Subjects With PKU. NCT00925054.
18. ClinicalTrials.gov. Long-Term Extension of Previous rAvPAL-PEG Protocols in Subjects With PKU (PAL-003). NCT00924703.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
For sapropterin: Removal of BH4 responsiveness at initial as this is evaluated via medication trial. Updated renewal criteria to allow continuation in those with neurocognitive improvement as per ACMG guidelines. Removed requirement of specialist prescribing upon renewal, this update is applicable to all agents.	03/2023
Added branded sapropterin dihydrochloride (Javygtor) to policy	11/2022
Addition of generic sapropterin dihydrochloride (generic Kuvan) into policy, requiring trial of generic prior to brand. Updates to QL, allowing for 60 mg max dose. Formatting updates and updates to supporting evidence.	10/2021
• Updated criteria to policy format and combined separate polices into one • Ensured sapropterin dihydrochloride (Kuvan) is not used in combination with pegvaliase (Palynziq) • Requirement of member requesting sapropterin dihydrochloride (Kuvan) to have tetrahydrobiopterin- (BH4-) responsive PKU • Added criteria to require documentation of current blood phenylalanine concentration and of current compliance with a phenylalanine restricted diet • Adjusted requirement of phenylalanine levels in use of sapropterin dihydrochloride (Kuvan) to be greater than 360 micromol/L for all ages • Updated renewal duration with Kuvan to 1 year to align with Palynziq	12/2019
pegvaliase (Palynziq) policy effective	08/2018
sapropterin dihydrochloride (Kuvan) policy effective	02/2009

Policy Type: PA/SP Pharmacy Coverage Policy: UMP020

Description

Sildenafil (Revatio, Liqrev), and tadalafil (Adcirca, Cialis, Alyq, Tadliq) are phosphodiesterase type 5 (PDE5) inhibitors.

Length of Authorization

- Initial: Length of benefit
- Renewal: Not applicable

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
sildenafil (Revatio)	Raynaud's phenomena Pulmonary arterial hypertension	20 mg tablets	90 tablets/30 days
		10 mg/mL suspension	224 mL/30 days (2 bottles)
sildenafil (Liqrev)	Pulmonary arterial hypertension	10 mg/ml oral suspension	122 mL/20 days
tadalafil (Cialis)	Benign prostatic hyperplasia	2.5 mg tablets	30 tablets/30 days
		5 mg tablets	
	Pulmonary arterial hypertension	20 mg tablets	60 tablets/30 days
tadalafil (Adcirca)	Pulmonary arterial hypertension	20 mg tablets	60 tablets/30 days
tadalafil (Alyq)	Pulmonary arterial hypertension	20 mg tablets	60 tablets/30 days
tadalafil (Tadliq)	Pulmonary arterial hypertension	20 mg/5 mL suspension	300 mL/30 days (2 bottles)

Initial Evaluation

I. Medication contained in this policy may be considered medically necessary when the following criteria below are met:
   A. A diagnosis of one of the following:
      1. **Pulmonary arterial hypertension (PAH)**; **AND**
         i. The medication is prescribed by or in consultation with a specialist (e.g., pulmonologist, cardiologist); **AND**
         ii. The patient is classified as having World Health Organization (WHO) Functional Class II-IV symptoms; **AND**
         iii. The request is for generic sildenafil tablets or generic tadalafil tablets; **OR**

a. The request is for Revatio tablets or Adcirca and both generic sildenafil and generic tadalafil are found to be ineffective, not tolerated, or contraindicated; **OR**
b. The request is for generic sildenafil oral suspension 10 mg/mL, and the member is unable to swallow oral tablets; **OR**
    i. The request is for brand Revatio oral suspension 10 mg/mL; **AND**
        1. generic sildenafil oral suspension 10 mg/mL, Tadliq oral suspension 20 mg/5mL, and Liqrev oral suspension 10 mg/mL have all been ineffective, not tolerated, or contraindicated; **OR**
    ii. The request is for Tadliq oral suspension 20 mg/5mL or Liqrev oral suspension 10 mg/mL; **AND**
        1. Generic sildenafil oral suspension 10 mg/mL has been ineffective, not tolerated, or contraindicated; **OR**

2. **Benign prostatic hyperplasia (BPH); AND**
    i. At least one alpha-1 blocker AND one 5-alpha-reductase inhibitor medication have been ineffective, not tolerated, or both are contraindicated
        a. Examples of 5-alpha reductase inhibitors: dutasteride, finasteride
        b. Examples of alpha-1 blockers: alfuzosin, doxazosin, silodosin, tamsulosin, terazosin; **AND**
    ii. Generic tadalafil 2.5 or 5 mg tablets are requested (please note, no other medications addressed in this policy are covered for BPH); **OR**
3. **Raynaud's disease/phenomena; AND**
    i. Generic sildenafil 20mg has been prescribed at a maximum quantity of 90 tablets per 30-day supply (please note, no other medications in this policy are covered for Raynaud's); **AND**
    ii. Treatment with a dihydropyridine calcium channel blocker (e.g., nifedipine, amlodipine, isradipine, felodipine) or diltiazem has been ineffective, not tolerated, or is contraindicated; **OR**
        a. Generic sildenafil 20mg tablets will be used in combination with a calcium channel blocker or diltiazem as additional treatment.

II. Medications listed in this policy are considered <u>not medically necessary</u> when criteria above are not met and/or when used for:
    A. Erectile dysfunction.

III. Medications listed in this policy are considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
    A. Traumatic brain injury
    B. Hypertension, not of the pulmonary atrial type
    C. Heart failure and/or other cardiovascular or central nervous system conditions, disorders, or diseases

D. Oncologic conditions
E. Encephalopathy
F. Cirrhosis

Renewal Evaluation

I. Renewal criteria - Not applicable, approval allowed for length of benefit.

Supporting Evidence

I. Pulmonary arterial hypertension: Pulmonary hypertension (PH) specific therapy is directed at the PH itself rather than the underlying cause of PH. Patients with persistent PH with World Health Organization (WHO) functional class II, III, or IV despite treatment of the underlying cause of PH should be evaluated for PH specific therapy. Group I patients should be observed and treated for the contributing factors. As of 2019, preferential treatments for group II-III patients include tadalafil plus other agents, and group IV should be treated with IV agents or double or triple combination therapy regimen that may or may not include tadalafil or sildenafil. Therapy is individualized to the patient and there are several suitable agents outside of sildenafil or tadalafil.
II. Benign prostatic hyperplasia (BPH): common treatment for BPH include alpha-1 adrenergic antagonists, 5-alpha-reductase inhibitors, anticholinergic agents, and phosphodiesterase-5 (PED-5) inhibitors. As of 2019, it was recommended that those with mild disease should be considered for an alpha-1 adrenergic antagonist. This is due to 5-alpha-reductase inhibitors requiring long-term treatment for efficacy (six to twelve months of treatment required prior to symptom improvement); however, it shall be noted that some patients will experience hypotension with alpha-1-adrenergic antagonists. Alternative options beyond these two classes include anticholinergic agents and PDE-5 inhibitors.
III. Raynaud phenomenon (RP): An exaggerated vascular response to cold temperature or emotional stress. This is manifested clinically by sharply demarcated color changes of the skin. Attacks occur commonly in the hands but may also occur in the toes, and attacks may cause symptoms such as numbness, clumsiness of the hand, aches, pains, or a feeling of pins and needles. Initial management of RP includes avoidance of triggers and vasoconstricting medications (e.g., nasal decongestants, amphetamines, ephedra, stimulants, triptans, ergotamines), as well as smoking cessation.
IV. Initial pharmacologic management of RP is recommended with calcium channel blockers of the dihydropyridine type. Amlodipine is preferred, but other such as nifedipine may be used. Other agents, such as PED-5 medications (e.g., sildenafil, tadalafil, vardenafil) may be considered with calcium channel blockers are contraindicated or not tolerated.

Investigational or Not Medically Necessary Uses

I. Erectile dysfunction treatment is deemed medically necessary by the plan and is excluded from coverage.

II. All of the aforementioned indications, conditions, diseases listed in the experimental/investigational section and treated with medications in this policy are being evaluated in clinical trials. Safety and efficacy have not yet been determined.

References

1. Oregon Insurance Division Bulletin INS 2014 – 1 Mental Health Parity
2. Diagnostic and Statistical Manual of Mental Disorder (DSM) Version IV-TR and V.
3. Bancroft J, Wu FC. Changes in erectile responsiveness during androgen replacement therapy. Arch Sex Behav. 1983;12(1):59-66.
4. UpToDate. Cunningham GR, Kadmon D. Medical treatment of benign prostatic hyperplasia. May 13, 2019. Available at: https://www.uptodate.com/contents/medical-treatment-of-benign-prostatic-hyperplasia?search=benign%20prostatic%20hyperplasia&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Accessed May 29, 2019.
5. UpToDate. Hopkins W, Rubin LJ. Treatment of pulmonary hypertension in adults. March 22, 2019. Available at: https://www.uptodate.com/contents/treatment-of-pulmonary-hypertension-in-adults?search=pulmonary%20hypertension&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2. Accessed May 29, 2019.
6. Barnes H, Brown Z, Burns A, Williams T. Phosphodiesterase 5 inhibitors for pulmonary hypertension. Cochrane Database Syst Rev. 2019;1:CD012621.
7. UpToDate. Wigley FM. Clinical manifestations and diagnosis of the Raynaud phenomenon. February 11, 2018. Available at: https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-the-raynaud-phenomenon?search=raynauds%20phenomena&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Accessed May 29, 2019.
8. UpToDate. Wigley FM. Treatment of Raynaud phenomenon: initial management. April 22, 2019. Available at: https://www.uptodate.com/contents/treatment-of-raynaud-phenomenon-initial-management?search=raynauds%20phenomena&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2. Accessed May 29, 2019.
9. Zidek W, Spiecker C, Knaup G, Steindl L, Breuer HW. Comparison of the efficacy and safety of nifedipine coat-core versus amlodipine in the treatment of patients with mild-to-moderate essential hypertension. Hypertension Study Group. Clin Ther. 1995;17(4):686-700.
10. Roustit M, Blaise S, Allanore Y, Carpentier PH, Caglayan E, Cracowski JL. Phosphodiesterase-5 inhibitors for the treatment of secondary Raynaud's phenomenon: systematic review and meta-analysis of randomised trials. Ann Rheum Dis. 2013;72(10):1696-9.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added Liqrev suspension into policy with a step through generic sildenafil suspension. Updated requirements of brand Revatio suspension to require step through generic product as well as Tadliq and Liqrev.	06/2023
Added tadliq suspension into policy criteria with a step through generic sildenafil suspension	11/2022
Added new product tadalafil (Tadliq) 20 mg/5 ml oral suspension	09/2022
Creation of policy from prior authorization criteria. Opened up criteria to allow for generic sildenafil and tadalafil for BPH and PAH due to generic availability.	05/2019
Updated PAH questions to remove contraindication questions, assess function classification of staging and trial and failure of generic sildenafil. Aligned with commercial PAH criteria. Added clinical note of Raynaud phenomena.	03/2018
Previous reviews	06/2015
Policy created	04/2015

Policy Type: PA/SP Pharmacy Coverage Policy: UMP053

Description

Pimavanserin (Nuplazid) is an orally administered is an atypical antipsychotic that works as a selective serotonin inverse agonist with an unknown mechanism of action.

Length of Authorization

- Initial: six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
pimavanserin (Nuplazid)	Parkinson's disease psychosis	34 mg capsules	30 capsules/30 days
		10 mg tablets	30 tablets/ 30 days

Initial Evaluation

I. **Pimavanserin (Nuplazid)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. The medication is prescribed by or in consultation with a neurologist; **AND**
   C. A diagnosis of **Parkinson's disease psychosis** with symptoms of hallucinations and delusions when the following are met:
      1. Symptoms of hallucinations and delusions have continued after reductions in current medications for Parkinson's disease or reductions in medications are not possible based on provider attestation; **AND**
      2. Treatment with clozapine or quetiapine has been ineffective or intolerable, unless both are contraindicated

II. Pimavanserin (Nuplazid) is considered investigational when used for all other conditions, including but not limited to the diagnosis of:
   A. Alzheimer's disease psychosis
   B. Schizophrenia
   C. Dementia related psychosis

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has experienced a reduction in delusions and hallucinations.

Supporting Evidence

I. There is a lack of safety and efficacy in the use of pimavanserin (Nuplazid) for those under the age of 18.
II. Due to the complexity around the diagnosis of Parkinson's disease (PD) and the treatment options, therapy should be prescribed by, or in consultation with, a neurologist.
III. Psychosis is a frequent complication of PD, occurring in up to 40% of patients, particularly those in the advanced stages of the disease due to the adverse effects of antiparkinsonian medications over time; mainly, the dopamine agonists. There is a recommended algorithm by the Movement Disorder Society to approaching treatment in these patients. Firstly, ruling out if psychosis is from an underlaying infection, and then assessing if the patient's psychosis is bothersome enough to warrant treatment. Treatment first begins with simply reducing or stopping PD medications if possible; if this is not possible or the symptoms continue, then initiating therapy with antipsychotic therapy (pimavanserin, quetiapine or clozapine) occurs.
IV. Pimavanserin (Nuplazid) was studied in a 6-week, randomized, placebo-controlled, parallel-group study in 199 patients with a diagnosis (PD) and psychotic symptoms (hallucinations and/or delusions) severe and frequent enough to warrant antipsychotic treatment. Patients were all 40 years or older with a documented PD history of at least one year; the majority of patients were on PD medications at the study start and were on stable doses at least 30 days prior to the start of the study.
V. The primary efficacy outcome was the change from baseline to week 6 in a PD-adapted scale for the assessment of positive symptoms (SAPS-PD). SAPS-PD is a 9-item scale adapted for PD from the Hallucinations and Delusions domains of the SAPS scale for schizophrenia. The SAPS-PD total score can range from 0 to 45 with higher scores reflecting greater severity of illness. A negative change in score indicates improvement.
VI. A positive effect was seen on both hallucination and delusion components of the SAPS-PD for pimavanserin (n=95) versus placebo (n=90) [-3.06 (95% CI -4.91, -1.2)]. No difference in motor function was observed between pimavanserin and placebo. Although statistically significant, the clinical relevance of this result is unclear.
VII. Pimavanserin (Nuplazid) also had an open-label extension (OLE) for patients completing one of the three double-blind, placebo-controlled studies. All patients received pimavanserin 34mg once daily for an additional four weeks of treatment. Efficacy results once again looked at SAPS-PD. Of 459 patients able to start the OLE, 424 patients continued in the trial for the four additional weeks. The SAPS-PD continued to show improvement during this four-week period, and those who originally were on placebo and switched over to pimavanserin showed the most positive effects during the OLE, having mean scores improving to the same level as the study arm group receiving pimavanserin during the double-blind trial.
VIII. In 2022, a long-term outcomes review was reported for pimavanserin for psychosis in clinical practice. A retrospective chart review was conducted at the Movement Disorders practice in

Providence, Rhode Island between 2016-2021 where 53 patients were identified as initiating pimavanserin, 45 of these patients had PD, and patients were on pimavanserin an average of 26 weeks. Initial improvement was seen in 47% of the group (25 of 53 patients). Due to inadequate control of symptoms with pimavanserin, an addition of another antipsychotic was needed to maintain a positive response for 10 of those 25 patients; whereas eight of the 25 patients were able to continue on pimavanserin for monotherapy.

IX. There are not head-to-head trials of the antipsychotic agents used in PD psychosis. Multiple systemic reviews and meta-analyses have been completed to address this. One in 2023, reviewed 19 studies evaluating atypical antipsychotics in a total of 1,242 patients with PD psychosis. Based on the Clinical Global Impression Scale for Severity, pimavanserin with a standardized mean difference (SMD) of -4.81 (95% CI -5.39,-4.24) and clozapine with a SMD of -4.25 (95% CI, -5.24, -3.26) both significantly improved symptoms compared to placebo.

X. The 2019 American Geriatrics Society Beers Panel recommends to generally avoid all antipsychotic medications in older patients with PD, with exceptions made for quetiapine, clozapine, and pimavanserin. The Movement Disorder Society rated clozapine as more efficacious compared to quetiapine, which was deemed to have insufficient evidence, and does not make any recommendation on pimavanserin (Nuplazid). An update was added one year later in 2019, discussing change in practice implications to the data on quetiapine, noting it was similarly efficacious to clozapine in a clozapine-controlled trial which did not have a placebo arm; updating quetiapine to possibly useful in PD-psychosis. There were no new comments to clozapine or pimavanserin regarding favoring one or the other.

Investigational or Not Medically Necessary Uses

I. Pimavanserin (Nuplazid) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   - A. Alzheimer's disease psychosis
     - i. The use in AD psychosis remains experimental at this time. In August of 2022, the FDA issued a complete response letter noting it could not approve the new indication at this time and recommended an additional trial in this space.
   - B. Schizophrenia
     - i. The use of pimavanserin in schizophrenia remains experimental at this time while a phase III trial continues.
   - C. Dementia related psychosis
     - i. A complete response letter was issued in April 2021 that "cited a lack of statistical significance in some of the subgroups of dementia and insufficient numbers of patients with certain less common dementia subtypes as lack of substantial evidence of effectiveness to support approval."

References

1. Pimavanserin (Nuplazid®) [Prescribing Information]. San Diego, CA: Acadia Pharmaceuticals, Inc. 11/2020.
2. Cummings J, Isaacson S, Mills R, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomized, placebo-controlled phase 3 trial. *Lancet.* 2014; 383: 533–40
3. Merims D, Balas M, Peretz C, Shabtai H, Giladi N. Rater-blinded, Prospective Comparison: Quetiapine Versus Clozapine for Parkinson's Disease Psychosis*. Clin Neuropharmacol*. 2006; 26:331-337.

4. Morgante L, Epifanio A, Spina E, et al. Quetiapine and Clozapine in Parkinsonian Patients with Dopaminergic Psychosis. *Clin Neuropharmacol*. 2004; 27:153-156.
5. Pollak P, Tison F, Rascol O, et al. Clozapine in drug induced psychosis in Parkinson's disease: a randomized, placebo controlled study with open follow up. *J Neurol Neurosurg Psychiatry.* 2004; 75:689–695.
6. Katzenschlager, R., Lloret, S. P., Weintraub, D., & Sampaio, C. (2019). Update on Treatments for Nonmotor Symptoms of Parkinson's Disease—An Evidence-Based Medicine Review. Movement Disorders, 34(2), 181.
7. UpToDate, Inc. Clinical manifestations of Parkinson disease. UpToDate [database online]. Waltham, MA. Updated 03/15/2023. Available at: http://www.uptodate.com/home/index.html. [Accessed 04/20/2023].
8. UpToDate, Inc. Management of nonmotor symptoms in Parkinson disease. UpToDate [database online]. Waltham, MA. Updated 01/20/2023. Available at: http://www.uptodate.com/home/index.html. [Accessed 04/18/2023].
9. Isaacson SH, Ballard CG, Kreitzman DL, et al. Efficacy results of pimavanserin from a multi-center, open-label extension study in Parkinson's disease psychosis patients. Parkinsonism Relat Disord. 2021 Jun;87:25-31. doi: 10.1016/j.parkreldis.2021.04.012. Epub 2021 Apr 28. PMID: 33933853.
10. Umer Akbar, Joseph H. Friedman, Long-term outcomes with pimavanserin for psychosis in clinical practice, Clinical Parkinsonism & Related Disorders, Volume 6, 2022, 100143, ISSN 2590-1125, https://doi.org/10.1016/j.prdoa.2022.100143.
11. Pahwa, R., Isaacson, S.H., Small, G.W. et al. Screening, Diagnosis, and Management of Parkinson's Disease Psychosis: Recommendations From an Expert Panel. Neurol Ther 11, 1571–1582 (2022). https://doi.org/10.1007/s40120-022-00388-y

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
istradefylline_Nourianz	Parkinson's Disease
levodopa_Inbrija	
apomorphine_Apokyn_Kynmobi	

Policy Implementation/Update:

Action and Summary of Changes	Date
Annual review; reformatted indication table, added in related policies, general formatting updates. Updated policy requirements to align with updated guidelines, addition of option to trial quetiapine OR clozapine. Updated supporting evidence to strengthen policy requirements.	11/2023
Transition from criteria to policy: Included requirements to attempt dose reduction in Parkinson's medications and specified what members must try and fail.	9/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP277

Split Fill Management*

Description

Pirtobrutinib (Jaypirca) is an orally administered non-covalent (i.e., reversable) Bruton Tyrosine Kinase inhibitor (BTKi).

Length of Authorization

- N/A

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
pirtobrutinib (Jaypirca)	Relapsed or refractory mantle cell lymphoma (R/R MCL) after at least two lines of systemic therapy including a BTKi Chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) after at least two prior lines of therapy including a BTK inhibitor and a BCL-2 inhibitor	100mg tablets	60 tablets/30 days
		50 mg tablets	30 tablets/ 30 days

**Quantity limit exceptions not allowed. 50mg dose is only to be used for dose modifications*

Initial Evaluation

I. **Pirtobrutinib (Jaypirca)** is considered investigational when used for all conditions, including but not limited to relapsed or refractory mantle cell lymphoma and chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

II. Pirtobrutinib (Jaypirca) is considered investigational when used for all other conditions, including but not limited to:
   A. Relapsed or refractory mantle cell lymphoma (MCL)
   B. Pirtobrutinib (Jaypirca) used in combination with another oncology therapy
   C. Mantle cell lymphoma (MCL)
   D. Chronic lymphocytic leukemia (CLL)
   E. Small lymphocytic lymphoma (SLL)
   F. Waldenström macroglobulinemia
   G. Marginal zone lymphoma

H. Chronic graft versus host disease

Renewal Evaluation

I. N/A

Supporting Evidence

I. Pirtobrutinib (Jaypirca) is a non-covalent (i.e., reversable) Bruton Tyrosine Kinase inhibitor (BTKi), FDA-approved under an accelerated approval pathway for the treatment of relapsed or refractory mantle cell lymphoma (R/R MCL) after at least two lines of systemic therapy, including a BTKi. Additionally, pirtobrutinib (Jaypirca) was approved under an accelerated approval pathway for the treatment of chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) after at least two prior lines of therapy including a BTK inhibitor and a BCL-2 inhibitor. Continued approval of pirtobrutinib (Jaypirca) is contingent upon verification of clinical benefit in confirmatory trials.
II. Safety and efficacy of pirtobrutinib (Jaypirca) has not been established in a pediatric population.
III. Efficacy and safety of pirtobrutinib (Jaypirca) in combination with other oncology agents has not been evaluated by clinical trials.
IV. The diagnosis and management of MCL and CLL/SLL requires detailed clinical examination in combination with advanced testing. Given the complexities of diagnosis and treatment of these conditions, supervision of treatment by an oncologist or hematologist is required.

Investigational or Not Medically Necessary Uses

I. There are ongoing clinical studies to assess efficacy and safety of pirtobrutinib (Jaypirca) in multiple settings. Pirtobrutinib (Jaypirca) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
    A. Pirtobrutinib (Jaypirca) used in combination with another oncology therapy
    B. Mantle cell lymphoma (MCL)
        i. The efficacy of pirtobrutinib (Jaypirca) in patients with relapsed or refractory MCL was based on an open-label, single-arm, phase 1/2 clinical trial (BRUIN). The trial enrolled patients (N=120) with relapsed or refractory MCL after at least two lines of systemic therapy, including a BTK inhibitor [ibrutinib (Imbruvica), acalabrutinib (Calquence), zanubrutinib (Brukinsa)]. Pirtobrutinib (Jaypirca) was administered as 200mg once a day. The primary efficacy outcome was objective response rate (ORR). Other measured outcomes included complete response (CR), partial response (PR), time to response, and duration of response. Pirtobrutinib (Jaypirca) showed an ORR of 50% (60) of patients. Fifteen (13%) achieved complete response with the remainder (38%) achieving partial response. Additionally, the time to response was 1.8 months (0.8-4.2) with a median duration of response of 8.3 months (5.7-NE).
        ii. The population was treatment experienced with a median of three prior lines of therapy, 93% having received two or more prior lines. All had previously received

a BTKi containing regimen; other prior therapies being chemo-immunotherapy (88%), HSCT (20%), lenalidomide (18%), CAR-T therapy (9%).

iii. The safety of pirtobrutinib (Jaypirca) was reported based on the pooled analyses from all cohorts in the phase 1/2 clinical trial. In the pooled safety population, the most common (≥ 20%) adverse reactions included decreased neutrophil count, hemoglobin, platelet count, lymphocyte count, as well as fatigue, musculoskeletal pain, bruising, and diarrhea. Severe adverse reactions specific to the MCL cohort occurred in 38% of patients which included pneumonia (14%), COVID-19 (4.7%), musculoskeletal pain (3.9%), hemorrhage (2.3%), pleural effusion (2.3%), and sepsis (2.3%). Dose reductions were seen in 4.7% of trial participants with therapy interruptions being needed in 32%. Nine percent of patients required permanent discontinuation. Fatal adverse reactions occurred in 7% of patients; most commonly due to infections (4.7%) including COVID-19 (3.1% of all patients). Current patient exposure to pirtobrutinib (Jaypirca) is limited to clinical trial participants; thus, the real-world safety profile and patient experience with this drug remain undefined. Based on a single-arm, open-label clinical trial in a small patient population, the overall safety profile of pirtobrutinib (Jaypirca) is largely unknown.

iv. The quality of the evidence is considered low given the observational nature of the trial with an open-label study design and lack of a comparator arm. Additionally, there remains an unknown clinical impact on the overall survival and health-related quality of life measures. Although overall response rate is an objective measure and may indicate the potential benefit of therapy, it does not predict long term outcomes such as overall survival.

v. As of March 2023, current third and subsequent line therapies for the treatment of R/R MCL are approved based on limited evidence. NCCN guideline directed therapies for third-line and beyond include brexucabtagene autoleucel (TECARTUS), pirtobrutinib (Jaypirca), and allogeneic HCT in eligible patients. Both CAR-T therapy and pirtobrutinib (Jaypirca) are FDA approved for R/R MCL under an accelerated approval pathway. Based on the limited available evidence, there is low confidence to direct to one therapy over another [i.e., brexucabtagene autoleucel (TECARTUS) versus pirtobrutinib (Jaypirca)].

vi. Due to lack of conclusive clinical data to direct a path to curative therapies, NCCN guidelines for MCL note that the best management for any patient with cancer is in a clinical trial setting, and participation in trial is especially encouraged. Patients participating in clinical trials receive regular care, often at leading health care facilities with experts in the field while participating in important medical research and further advancements in treatment, with close safety monitoring and follow-up. Participation in a clinical trial remains the most favorable treatment option for patients with R/R MCL. Despite the accelerated FDA-approval, continued approval of pirtobrutinib (Jaypirca) as a subsequent-line treatment of MCL, remains contingent upon verification of clinical benefit in confirmatory trials. Additionally, an expanded access program via manufacturer, as part of the ongoing clinical

studies of pirtobrutinib (Jaypirca), remains a practical option and an alternative path to treatment for qualifying patients.

C. Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)
    i. The efficacy of pirtobrutinib (Jaypirca) in patients with previously treated CLL/SLL was based on an open-label, single-arm, phase 1/2 arm of a larger clinical trial (BRUIN). The trial enrolled patients (N=108) with CLL/SLL after at least two lines of systemic therapy, including a BTK inhibitor [ibrutinib (Imbruvica), acalabrutinib (Calquence), zanubrutinib (Brukinsa)] and a BCL2 inhibitor. Pirtobrutinib (Jaypirca) was administered as 200mg once a day. The population was treatment experienced with a median of five prior lines of therapy (2-11). All had previously received a BTKi containing regimen [ibrutinib (Imbruvica) (97%), acalabrutinib (Calquence) (9%), zanubrutinib (Brukinsa) (0.9%)] and a BCL-2 inhibitor [venetoclax (Venclexta)].
    ii. The primary efficacy outcome was objective response rate (ORR). Other measured outcomes included complete response (CR), partial response (PR), progression free survival (PFS), time to response, and duration of response. Pirtobrutinib (Jaypirca) had an ORR of 70.0% (95% CI, 60.0 to 78.8) and 79.0% (95% CI, 69.7 to 86.5) when partial response with lymphocytosis was included. No patients in this subgroup were able to achieve a complete response. Additionally, the median time to response was 3.7 months (1.7-27.9) with a median duration of response of 12.2 months (9.3-14.7). Median PFS was 17 months.
    iii. The most common adverse reactions (≥ 20%), excluding laboratory terms, were fatigue, bruising, cough, musculoskeletal pain, COVID-19, diarrhea, pneumonia, abdominal pain, dyspnea, hemorrhage, edema, nausea, pyrexia, and headache. Adverse events of special interest included infections (71%), bleeding (42.6%), and neutropenia (32.5%). The incidence of infection while on pirtobrutinib was higher than with other BTK inhibitors in this cancer type (71% vs 55.6%). Treatment-related adverse events led to dose reductions in 15 patients (4.7%) and permanent discontinuation of pirtobrutinib in nine patients (2.8%).
    iv. In total, 18 patients died while receiving pirtobrutinib (Jaypirca). Two died from disease progression. The remaining 16 succumbed to other causes including coronavirus disease 2019 (Covid-19) or Covid-19–related pneumonia (8 patients), pneumonia or fungal pneumonia (2 patients), septic shock or shock (2 patients), and other causes (4 patients).
    v. NCCN guidelines recommend use of pirtobrutinib (Jaypirca) for use in certain circumstances should there be resistance or intolerance to prior covalent BTKi therapy. Additionally, it remains as a therapy for relapsed or refractory disease after prior BTKi and venetoclax-based regimens. Use in the both of the settings above carry a category 2A recommendation. The FDA labeled indication specifically states pirtobrutinib (Jaypirca) is for use after therapy with a BTKi and BCL-2 inhibitor. Despite the accelerated FDA-approval, continued approval of pirtobrutinib (Jaypirca) as a subsequent-line treatment of CLL/SLL, remains contingent upon verification of clinical benefit in confirmatory trials.

vi. The quality of the evidence is considered low given the observational nature of the trial with an open-label study design and lack of a comparator arm. Additionally, there remains an unknown clinical impact on the overall survival and health-related quality of life measures. Although overall response rate is an objective measure and may indicate the potential benefit of therapy, it does not predict long term outcomes such as overall survival. Other outcomes measured including PFS may be considered the "gold standard" in this disease state, though other publications consider PFS an "unreliable survival surrogate" as patients with CLL/SLL have increased comorbidities given it is a disease of the mostly elderly who generally succumb to other conditions without disease progression.

D. Waldenström macroglobulinemia
E. Marginal zone lymphoma
F. Chronic graft versus host disease

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Jaypirca. Package Insert. Lilly USA LLC; January 2023.
2. Mato AR, Shah NN, Jurczak W, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. Lancet. 2021;397(10277):892-901. doi:10.1016/S0140-6736(21)00224-5
3. National Comprehensive Cancer Network. B-Cell Lymphoma. NCCN. February 8, 2023. Accessed February 9, 2023. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf
4. Cohen JB, Shah NN, Alencar AJ, et al. MCL-133 Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Previously Treated Mantle Cell Lymphoma: Updated Results From the Phase 1/2 BRUIN Study. Clin Lymphoma Myeloma Leuk. 2022;22 Suppl 2:S394-S395. doi:10.1016/S2152-2650(22)01569-5
5. Lilly. U.S. FDA Approves Jaypirca™ (pirtobrutinib), the First and Only Non-Covalent (Reversible) BTK Inhibitor, for Adult Patients with Relapsed or Refractory Mantle Cell Lymphoma After at Least Two Lines of Systemic Therapy, Including a BTK Inhibitor. Updated January 27, 2023. Accessed January 30, 2023.
6. Pirtobrutinib (Jaypirca) product dossier. Eli Lilly and Company. February 1, 2023.
7. Mato AR, Woyach JA, Brown JR, et al. Pirtobrutinib after a Covalent BTK Inhibitor in Chronic Lymphocytic Leukemia. N Engl J Med. 2023;389(1):33-44. doi:10.1056/NEJMoa2300696
8. National Comprehensive Cancer Network. B-Cell Lymphoma. NCCN. March 11, 2024. Accessed March 24, 2024. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf
9. US Food and Drug Administration. FDA grants accelerated approval to pirtobrutinib for chronic lymphocytic leukemia and small lymphocytic lymphoma. FDA.gov. December 7, 2023. Accessed March 13, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pirtobrutinib-chronic-lymphocytic-leukemia-and-small-lymphocytic

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
acalabrutinib (Calquence®) Policy	Mantle cell lymphoma (previously treated)
	Chronic lymphocytic leukemia (CLL)
	Small lymphocytic lymphoma (SLL)
ibrutinib (IMBRUVICA®) Policy	Mantle cell lymphoma (previously treated)
	Marginal zone lymphoma (relapsed/refractory)
	Chronic graft-versus-host disease (refractory)
	Chronic lymphocytic leukemia/Small lymphocytic lymphoma
	Waldenström macroglobulinemia
zanubrutinib (Brukinsa™) Policy	Mantle cell lymphoma
	Waldenström macroglobulinemia
	Chronic lymphocytic leukemia/Small lymphocytic lymphoma
	Relapsed or refractory marginal zone lymphoma in adults who have received at least one anti-CD20-based regimen
venetoclax (Venclexta®) Policy	Chronic lymphocytic leukemia/Small lymphocytic lymphoma
	Acute myeloid leukemia
duvelisib (Copiktra®) Policy	Relapsed/refractory chronic lymphocytic leukemia (CLL)
	Relapsed/refractory small lymphocytic lymphoma (SLL)
idelalisib (Zydelig®) Policy	Relapsed Chronic Lymphocytic Leukemia (CLL)
lenalidomide (Revlimid®), pomalidomide (Pomalyst®), thalidomide (Thalomid®) Policy	Follicular lymphoma
	Mantle cell lymphoma
	Marginal zone lymphoma
	Multiple myeloma
	Multiple myeloma maintenance therapy following auto-HSCT
	Myelodysplastic syndromes

Policy Implementation/Update:

Action and Summary of Changes	Date
Added SLL/CLL indication to E/I section with supporting evidence. Moved R/R MCL supporting evidence to E/I section. Updated related policies table.	4/2024
Policy created	05/2023

Policy Type: PA/SP Pharmacy Coverage Policy: UMP225

Split Fill Management*

Description

Ponatinib (Iclusig) is an orally administered tyrosine kinase inhibitor with activity against unmutated and mutated BCR-ABL including the threonine-to-isoleucine mutation at position 315 (T315I).

Length of Authorization

- Initial: three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication*	Quantity Limit
ponatinib (Iclusig)	10 mg tablet	CP-CML with resistance or intolerance to two prior kinase inhibitors; AP-CML, BP-CML, and Ph+ ALL for whom no other kinase inhibitors are indicated; T315I-positive CML (any phase) or T315I-positive Ph+ ALL	30 tablets/30 days
	15 mg tablet		30 tablets/30 days
	30 mg tablet		30 tablets/30 days
	45 mg tablet		30 tablets/30 days

*CML = chronic myeloid leukemia, CP = chronic phase, AP = accelerated phase, BP = blast phase, Ph+ = Philadelphia chromosome positive, ALL = acute lymphoblastic leukemia

Initial Evaluation

I. Ponatinib (Iclusig) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   C. Medication is not used in combination with any other oncology therapy; **AND**
   D. A diagnosis of **Chronic Phase-Chronic Myeloid Leukemia (CP-CML); AND**
      1. Documented resistance, or intolerance to, two prior tyrosine kinase inhibitors (TKIs) (e.g., dasatinib (Sprycel), imatinib (Gleevec), nilotinib (Tasigna), bosutinib (Bosulif); **OR**
      2. Documented positive T315I mutation
   E. A diagnosis of **Accelerated Phase- Chronic Myeloid Leukemia (AP-CML), Blast Phase-Chronic Myeloid Leukemia (BP-CML), or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ALL); AND**

1. Provider attestation that all other TKIs used to treat AP-CML, BP-CML, or Ph+ALL (e.g., dasatinib (Sprycel), imatinib (Gleevec), nilotinib (Tasigna), bosutinib (Bosulif) have been ineffective, not tolerated, contraindicated or not indicated; **OR**
2. Documented positive T315I mutation

I. Ponatinib (Iclusig) is considered investigational when used for all other conditions, including but not limited to:
   A. Newly diagnosed CP-CML

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If this applies, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Will not be used with any other oncology therapy; **AND**
IV. Disease response to treatment defined by stabilization of disease or decrease in rate of disease progression.

Supporting Evidence

I. Ponatinib (Iclusig) is an oral tyrosine kinase inhibitor with activity against unmutated and mutated BCR-ABL, including the threonine-to-isoleucine mutation at position 315 (T315I), which is present in around 20% of patients with tyrosine kinase inhibitor-resistant disease.
II. Ponatinib (Iclusig) carries three FDA approved indications and is used in the treatment of patients with chronic phase (CP) chronic myeloid leukemia (CML) with resistance or intolerance to at least two prior kinase inhibitors, accelerated phase (AP) or blast phase (BP) CML, Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom no other kinase inhibitors are indicated, and T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Ph+ ALL.
III. The original FDA approval for ponatinib (Iclusig) took place in 2012 and was based on the PACE clinical trial which evaluated safety and efficacy of ponatinib (Iclusig). Post-marketing studies submitted to the FDA included a 5 year follow up PACE study and an ongoing OPTIC clinical trial, which informed of the optimal dosing in patients with CP-CML.
IV. The PACE clinical trial was an open label, single arm, phase II study in adult subjects with CML (all phases) or Ph+ ALL with resistance/intolerance to dasatinib or nilotinib, or development of T315I mutation after tyrosine kinase inhibitor (TKI) therapy. There were 270 subjects in CP-CML, 85 subjects in AP-CML, 62 subjects in BP-CML, and 62 subjects in Ph+ALL. These subjects were further randomized based on T315I mutation status. Nearly one-third of subjects (29%) had the T315I mutation. The primary efficacy endpoint of major cytogenic response (MCyR) by 12 months of treatment was met in 51% of those with resistance or intolerance to prior TKI therapy and in 70% of those with a positive T315I mutation status in the CP-CML cohort. In AP-CML, BP-CML, and Ph+ALL the primary endpoint was major hematologic response (MaHR) by 6 months of treatment which was met in 57% of those with prior resistance or intolerance to TKI therapy and in 50% of those with a positive T315I mutation status in the AP-CML cohort. MaHR was met in

35% of those with resistance or intolerance to prior TKI therapy and in 33% of those with a positive T315I mutation status in the BP-CML/Ph+ALL cohort.

V. The five year follow up study of ponatinib (Iclusig) demonstrated a continued clinical benefit in patients with heavily treated CML or Ph+ALL. The types of adverse events reported were generally similar to those reported previously and included rash (47%), abdominal pain (46%), thrombocytopenia (46%), headache (43%), and constipation (41%). Dose related adverse events included cardiovascular, cerebrovascular, and peripheral vascular events. The cumulative incidence of arterial occlusive events (AOEs) was 25% in the overall population (serious AOEs, 20%) and 31% in the CP-CML population (serious AOEs, 26%); higher cumulative incidence in CP-CML correlates with the longer duration of treatment.

VI. OPTIC is an ongoing phase 2, open label, randomized, multicenter clinical trial evaluating response-based dosing regimens of ponatinib (Iclusig) with the aim of optimizing its efficacy and safety in patients with CP-CML who are resistant or intolerant to prior TKI therapy. Interim results at 21 months of follow up show benefit of ponatinib (Iclusig) in all three dosing regimens studied (15 mg, 30 mg, and 45 mg), with the 45 mg starting dose showing greatest efficacy results. Thus far, the FDA has made recommendations to start with the 45 mg dose which could subsequently be titrated down to 15 mg upon achievement of <1% BCR-ABL1. Primary analysis will provide a refined understanding of the benefit: risk profile of three different starting doses of ponatinib (Iclusig).

VII. For the treatment of Ph+ALL, current NCCN guidelines recommend dasatinib (Sprycel) and imatinib (Gleevec) as the preferred agents as well as other TKIs such as bosutinib (Bosulif), nilotinib (Tasigna), or ponatinib (Iclusig). Moreover, certain TKIs are contraindicated with specific BCR-ABL1 mutations; ponatinib (Iclusig) is the only TKI without any contraindicated mutations.

VIII. For the treatment of CP-CML, current NCCN guidelines recommend the following agents depending on the patient's risk score and mutation profile: imatinib (Gleevec), bosutinib (Bosulif), dasatinib (Sprycel), nilotinib (Tasigna), or ponatinib (Iclusig) when there's resistance to two prior TKIs. For the treatment of AP-CML and BP-CML, preferred regimens include bosutinib (Bosulif), dasatinib (Sprycel), nilotinib (Tasigna), or ponatinib (Iclusig) with omacetaxine (Synribo) cited as being useful in certain circumstances.

Investigational or Not Medically Necessary Uses

I. Ponatinib (Iclusig) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Newly diagnosed CP-CML
      i. Ponatinib (Iclusig) was studied as a first line agent in patients newly diagnosed with CP-CML and showed an increase in risk of serious adverse reactions 2-fold compared to imatinib (Gleevec) 400 mg once daily. This prospective randomized clinical trial was subsequently halted for safety. Ponatinib (Iclusig) treated patients exhibited a greater incidence of myelosuppression, pancreatitis, hepatotoxicity, cardiac failure, hypertension, and skin and subcutaneous tissue disorders. Ponatinib (Iclusig) is not indicated and is not recommended for the treatment of patients with newly diagnosed CP-CML.

medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.

References

1. ICLUSIG (ponatinib) [package insert]. Cambridge, MA: ARIAD Pharmaceuticals, Inc.; December 2020.
2. NCCN Guidelines. Chronic Myeloid Leukemia. Version 3.2021-January 13, 2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cml_blocks.pdf. Accessed on March 7, 2021.
3. NCCN Guidelines. Acute Lymphoblastic Leukemia. Version 2.2020-October 23, 2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/all_blocks.pdf. Accessed on March 7, 2021.
4. Cortes, Jorge E et al. "Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial." Blood vol. 132,4 (2018): 393-404. doi:10.1182/blood-2016-09-739086
5. Cortes, Jorge E et al. "A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias." The New England journal of medicine vol. 369,19 (2013): 1783-96. doi:10.1056/NEJMoa1306494

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy criteria transitioned to a new format; criteria changes include the removal of laboratory monitoring requirements (blood counts, hepatic enzyme tests, serum lipase) and monitoring of atrial thrombotic events, addition of a new dosage forms 10 mg and 30 mg tablets, and addition of requiring two prior TKIs in CP-CML, consistent with the FDA labeling change.	03/2021
Policy criteria created	05/2013

Policy Type: PA/SP Pharmacy Coverage Policy: UMP220

Split Fill Management*

Description

Pralsetinib (Gavreto) is an orally administered kinase inhibitor of RET.

Length of Authorization

- N/A

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
pralsetinib (Gavreto)	RET Fusion-Positive Non-Small Cell Lung Cancer; RET Fusion-Positive Thyroid Cancer, in those that are radioactive iodine refractory	100 mg capsules	120 capsules/30 days

Initial Evaluation

I. **Pralsetinib (Gavreto)** is considered not medically necessary when used for RET fusion-positive medullary thyroid cancer and investigational when used for all other indications, including but not limited to Non-Small Cell Lung Cancer (NSCLC) and Thyroid Cancer.

Renewal Evaluation

I. N/A

Supporting Evidence

I. RET, a transmembrane receptor protein, is present at the surface of several tissue types. Alterations include fusions and point mutations – both are oncogenic drivers.
II. Pralsetinib (Gavreto) was evaluated in one Phase 1/2, dose expansion and escalation, multi-cohort, open-label, single-arm trial. Interim results showed potential antitumor activity via overall response rate (ORR) and duration of response (DoR). The primary outcome is ORR, and the secondary outcomes include DoR and proportion of patients with DoR six months or greater.
III. For RET fusion-positive NSCLC: Patients with advanced or metastatic disease that were either treatment naïve (n=27) or progressed on platinum-based chemotherapy (n=87) were assessed. For RET-mutant MTC, patients were either treatment naïve (n=29) or progressed on cabozantinib (Cometriq) or vandetanib (Caprelsa) (n=55). All patients had progressed on standard of care for RET-fusion-positive TC (n=9).

Clinical Efficacy in Pretreated Patients			
Outcome	**RET Fusion+ NSCLC (n=87)**	**RET-Mutant MTC (n=55)**	**RET Fusion-Positive TC (n=9)**
ORR (%)	57% (46, 68)	60% (46, 73)	89% (52, 100)
CR (%)	5.7%	1.8%	0
PR (%)	52%	58%	89%
DoR (mo)	NR (15.2-NE)	NR (15.1, NE)	NR (NE, NE)
DoR ≥ 6 mo (%)	80%	79%	100%
Clinical Efficacy in Treatment-Naïve Patients			
Outcome	**RET Fusion+ NSCLC (n=27)**	**RET-Mutant MTC (n=29)**	**RET Fusion-Positive TC***
ORR (%)	70% (50, 86)	66% (46, 82)	N/A
CR (%)	11%	10%	
PR (%)	59%	55%	
DoR (mo)	9 (6.3-NE)	NR (NE, NE)	
DoR ≥ 6 mo (%)	58%	84%	

*All patients were refractory to standard therapy.

IV. The quality of the evidence is considered low given the open-label and single-arm trial design and small sample size; thus, true medication efficacy remains uncertain given the nature of observational data. Additionally, outcomes such as ORR and DoR have not been correlated with clinically meaningful outcomes such as improved survival or quality of life.

V. Phase 3 trial, AcceleRET, is planned to evaluate pralsetinib (Gavreto) in advanced or metastatic, RET fusion-positive NSCLC versus platinum-based chemotherapy. It will be evaluated in an open-label, randomized trial for first-line metastatic systemic therapy. Outcomes of interest include PFS, OS, time to intracranial progression, and quality of life. This international trial has a target enrollment of 250 patients, with an estimated completion date of November 2024.

VI. Pralsetinib (Gavreto) was initially approved under accelerated approval for RET fusion-positive NSCLC, advanced or metastatic. The conversion to regular approval was based on data from an additional 123 patients and 25 months of additional follow-up to assess durability of response. A total of 237 participants with locally advanced or metastatic RET fusion-positive NSCLC demonstrated an ORR of 78% (95% CI: 68, 85) with a median DOR of 13.4 months (95% CI: 9.4, 23.1). Among 130 patients previously treated with platinum-based chemotherapy, ORR was 63% (95% CI: 54, 71) with a median DOR of 38.8 months (95% CI: 14.8, not estimable). NCCN guidelines include pralsetinib (Gavreto) and selpercatinib (Retevmo) as preferred first-line and subsequent-line therapy (category 2a). Cabozantinib (Cometriq) is listed as useful in certain circumstances (category 2a) and vandetanib (Caprelsa) was recently removed as a treatment option.

VII. RET fusion-positive thyroid cancer: NCCN recommends radioactive iodine as first line therapy. In those not amenable to RAI, treatment options include selpercatinib (Retevmo) (category 1) and pralsetinib (category 2B).

VIII. Pralsetinib (Gavreto) was previously approved under an accelerated pathway for treatment of advanced or metastatic RET-mutant medullary thyroid cancer (MTC) in patients aged 12 years and older. In June 2023, the manufacturer was unable to provide confirmatory MTC study results to fulfill the FDA post marketing requirement and voluntarily withdrawn this indication from the market. This decision is not based on efficacy or safety of pralsetinib and does not affect other approved indications.

IX. Safety data is based on a pooled population of 438 patients. Common adverse events (AE) that occurred ≥15% or more of the population: fatigue, constipation, musculoskeletal pain, hypertension, edema, diarrhea, dry mouth, cough, and pneumonia. Serious AE that occurred ≥2%: pneumonia, sepsis, UTI, pyrexia, increased ALT/AST, and phosphatase, and decreased lymphocytes, neutrophils, hemoglobin, phosphate, calcium, sodium, and platelets. Fatal AE

occurred in 5% of patients (pneumonia and sepsis) in the NSCLC cohort. Warnings and precautions: interstitial lung disease, hypertension, hepatotoxicity, hemorrhage, tumor lysis syndrome, impaired wound healing, and embryo-fetal toxicity.

X. Dose reductions due to AE occurred in up to 67% of patient, which varied by cohort. Dose reductions occurred in up to 44%, and permanent discontinuation rate in up to 15%. The true safety profile of pralsetinib (Gavreto) remains unknown given the observational evaluation.

XI. Insight from oncology specialists indicate that the diagnosis of stage IV metastatic disease can include intra-pulmonary (disease contained within the lungs) and extra-pulmonary (disease spread to organs outside the lungs) metastases. Intra-pulmonary metastases are typically staged as M1a and described as one of the following situations: separate nodule in the other lung, pleural or pericardial nodules, or malignant pleural or pericardial effusions. The treatment approach for those with intra-pulmonary metastases should be individualized and include surgery and, when surgery is not feasible, standard systemic therapy.

XII. Ongoing research focuses on identifying potential novel biomarkers and mechanisms involved in resistance to these therapies. In this regard, conventional chemotherapy agents may remain practical and established therapeutic options for members, after progression on or after first-line therapies (e.g., platinum-based chemotherapy). Due to lack of conclusive clinical data to direct a path to curative therapies, NCCN guidelines for the treatment of majority of cancer types (e.g., NSCLC, cholangiocarcinoma, neuroendocrine, sarcoma) note that the best management for any patient with cancer is in a clinical trial setting, and participation in trial is especially encouraged. Patients participating in clinical trials receive regular care, often at leading health care facilities with experts in the field while participating in important medical research and further advancements in treatment, with close safety monitoring and follow-up. Participation in a clinical trial remains the most favorable treatment option for patients with advanced NSCLC. Despite the accelerated FDA-approval, and category 2A recommendations from NCCN, continued approval of selpercatinib (Retevmo) as a subsequent-line treatment of tumors harboring RET fusions in thyroid cancer refractory to radioactive iodine, remains contingent upon verification of clinical benefit in confirmatory trials.

Investigational or Not Medically Necessary Uses

I. Pralsetinib (Gavreto) in treatment of RET fusion-positive medullary thyroid cancer (MTC) is being withdrawn based on the confirmatory Phase III randomized AcceleRET study, which did not meet its primary endpoint and thus did not fulfill the confirmatory data requirements of the Accelerated Approval granted by the U.S. FDA nor the conditional marketing approvals granted in other countries. Genetech is working with the FDA towards the withdrawal of this indication.

II. Pralsetinib (Gavreto) has not yet been sufficiently studied for safety and efficacy for any condition.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Gavreto (pralsetinib) [prescribing information]. South San Francisco, CA: Genentech Inc; June 2023.
2. Retevmo [Prescribing Information]. Eli Lilly and Company. Indianapolis, IN. May 2020.
3. Adeniran AJ, Ahu Z, Gandhi M, et al. Correlation between genetic alterations and microscopic features, clinical manifestations, and prognostic characteristics of thyroid papillary carcinomas. Am J Surg Pathol. 2006. 30(2): 216-222.
4. Drilon A, Hu ZI, Lai GGY, Tan DSW. Targeting RET-driven cancers: lessons from evolving preclinical and clinical landscapes. Nat Rev Clin Oncol. 2018a Mar;15(3):151-67.
5. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer Treatment Guidelines V2.2024. February 9, 2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
6. National Comprehensive Cancer Network. Thyroid Carcinoma Guidelines V1.2024. February 1, 2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf
7. European Society for Medical Oncology. Metastatic non-small-cell lung cancer. ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. September 15, 2020.
8. FDA Approves Pralsetinib for Non-Small Cell Lung Cancer with RET Gene Fusions. FDA.gov, August 9, 2023.Available at https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pralsetinib-non-small-cell-lung-cancer-ret-gene-fusions

Related Policies

Policy Name	Disease state
selpercatinib (Retevmo)	RET Fusion-Positive Non-Small Cell Lung Cancer; RET-Mutant Medullary Thyroid Cancer; RET Fusion-Positive Thyroid Cancer, in those that are radioactive iodine refractory
cabozantinib (Cabometyx, Cometriq)	Progressive or metastatic medullary thyroid carcinoma
vandetanib (Caprelsa)	Locally advanced or metastatic medullary thyroid cancer
Multi-Targeted Tyrosine Kinase Inhibitors (Multi-TKI)	

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated supporting evidence to include extension study results to change FDA approval of pralsetinib (Gavreto) from accelerated to traditional in treatment of NSCLC and updated NCCN guideline recommendations. Moved RET-positive fusion MTC from covered indication to non-medically necessary due to withdrawn indication.	3/2024
Added supporting evidence around stage IV metastatic disease and metastases.	10/2021
Policy created	02/2021

Policy Type: PA Pharmacy Coverage Policy: UMP283

Description

Prescription digital therapeutics (PDTs) are devices, internet applications or other software-based technology intended for the prevention, management, or treatment of a medical condition. PDTs are cleared, authorized, or approved under section 510(k), 513(f)(22), or 515 of the federal food, drug, and cosmetic act, and must be prescribed by a licensed healthcare provider. The purpose of this policy is to ensure the appropriate use of these interventions.

Length of Authorization

- Initial:
  i. Somryst: one time authorization to cover up to 9-week treatment
  ii. EndeavorRx: NA
- Renewal:
  i. Somryst: not applicable; this is a single one-time treatment
  ii. EndeavorRx: NA

Prescription Digital Therapeutics (PDTs) included in this Policy

Product Name	Indication	Quantity Limit
Somryst*	Chronic Insomnia	1 x access, up to 9-week treatment
EndeavorRx	Attention Deficit and Hyperactivity Disorder (ADHD)	One activation code/30 days

** Somryst NDC 96439-0030-01*

Initial Evaluation

I. **Somryst (digital therapy)** may be considered medically necessary when the following criteria are met:
   A. Member is 22 years of age or older; **AND**
   B. A diagnosis of **chronic insomnia**; **AND**
      1. Attestation by provider that all the following are met:
         i. Member is under their supervision; **AND**
         ii. Member is able to read and understand English; **AND**
         iii. Member is familiar with how to use mobile apps; **AND**
      2. Attestation by provider member's daily life or work does not require them to be highly alert or cautious (e.g., long-haul truck drivers, long-distance bus drivers, air traffic controllers, operators of heavy machinery, certain assembly line jobs)

II. **EndeavorRx** is not covered by the pharmacy benefit.

I. Somryst and EndeavorRx are considered investigational when used for all other conditions, including but not limited to:
   A. Short-term insomnia
   B. Parasomnia
   C. When used as a stand-alone therapy
   D. Cognitive function improvement in disease conditions other than ADHD (e.g., autism spectrum disorder, systemic lupus erythematosus [SLE])
   E. Sensory processing disorder

Renewal Evaluation

I. Somryst:
   A. Not applicable. Somryst is a one-time 9-week treatment.
II. EndeavorRx:
   A. Not applicable. EndeavorRx is not covered by the pharmacy benefit.

Supporting Evidence

Somryst:

I. The American Academy of Sleep Medicine (AASM) strongly recommends cognitive behavioral therapy for insomnia (CBT-I) as part of the initial recommended approaches to treat chronic insomnia in adults.
   - CBT-I combines one or more cognitive therapies, alongside education about sleep regulation, stimulus control, and sleep restriction therapy. This can also include sleep hygiene education, relaxation training, and use of sleep diaries.
   - CBT-I is digitally delivered via the Somryst app on a tablet or smartphone.

II. While cognitive behavioral therapy is the standard of care in the treatment of insomnia, the FDA authorization of Somryst was based on a controlled study where CBT-I was delivered by a computer. Thirty-four subjects were randomized to receive either control (sleep diary) or computer-based CBT-I. The CBT-I treatment group had a statistically significant difference in improved sleep versus control.
III. Somryst is indicated in patients 22 years of age and older with chronic insomnia. Product claim includes improving insomnia symptoms.
IV. Somryst use is intended as a single 9-week treatment, under the supervision of a provider.
V. Somryst guides the user through various activities and modules over 6 to 9 weeks; there is no data to support repeat use or use beyond this time.
VI. Since CBT-I is delivered via a digital means on a tablet or smartphone, safe and typical use requires familiarity with apps and ability to read and understand English.
VII. Treatment with Somryst includes both sleep restriction and consolidation which can cause sleepiness, especially in the early stages of using this prescribed digital therapeutic. For individuals who must be alert or cautious to avoid serious accidents in their job or daily life, Somryst should not be used. Examples include: long-haul truck drivers, long-distance bus drivers, air traffic controllers, those who operate heavy machinery or select assembly line work.

EndeavorRx:

VIII. EndeavorRx (Akili Interactive Labs, Inc.) is an FDA-authorized Prescription Digital Therapeutic (PDT) indicated to improve attention function in children eight to 12 years of age with attention-

deficit hyperactivity disorder (ADHD). Delivered via an action video game experience, one prescription of EndeavorRx provides 30 days of access and is administered daily (25 minutes, five days/ week).

IX. Utility of EndeavorRx has been assessed in the improvement of attention function as measured by computer-based testing in children ages eight to 12 years old with primarily inattentive or combined-type ADHD, who have a demonstrated attention issue. During clinical trials, patients who engaged with EndeavorRx demonstrated improvements in a digitally assessed measure, (Test of Variables of Attention [TOVA]), of sustained and selective attention. Patients using EndeavorRx may not display benefits in typical behavioral symptoms, such as hyperactivity. EndeavorRx should be considered for use as part of a therapeutic program that may include clinician-directed therapy, medication, and/or educational programs, which further address symptoms of the disorder.

X. Although there are no contraindications noted to the use of EndeavorRx, this PDT may not be appropriate for patients with photo-sensitive epilepsy, color blindness, or physical limitations that restrict the use of a mobile device.

XI. Treatment recommendations for patients with ADHD vary based on age and include behavioral changes, cognitive therapy, and pharmacotherapy. Pharmacotherapy options include stimulants (e.g., methylphenidate and amphetamines) and non-stimulants (e.g., guanfacine, atomoxetine). The American Academy of Pediatrics (AAP) ADHD guidelines recommend parent training in behavior management (PTBM) and behavioral classroom interventions as the first-line treatment for children under 12 years of age. Additionally, for children six years and above, the addition of pharmacotherapy may be considered.

XII. EndeavorRx is the first PDT for the treatment of ADHD in children and was FDA-authorized via a *de novo* pathway. It may be considered an adjunct therapy combined with PTBM, clinician-directed behavioral therapy, and pharmacotherapy. EndeavorRx is not recommended to be used as a stand-alone therapy or as a substitute for pharmacotherapy. As of June 2023, The AAP guideline has not been updated to include EndeavorRx as a treatment option for ADHD.

XIII. EndeavorRx was assessed via two clinical trials, STARS-ADHD, a phase 3, randomized (1:1), double-blind clinical trial, which assessed response to EndeavorRx versus a digital sham control; and STARS-ADJUNCT, an open-label, dual-cohort trial which assessed EndeavorRx as an adjunct to stimulant therapy. STARS-ADHD included patients (N=348) aged eight to 12 years with baseline ADHD rating scale score (ADHD-RS-IV) ≥28, and Test of Variables of Attention - Attentional Performance Index (TOVA-API) ≤-1.8. Mean change in TOVA-API from baseline to day 28 was assessed as the primary outcome. STARS-ADJUNCT trial included patients (N= 236), eight to 14 years of age who were assigned to an on-stimulant cohort (n= 130) or a non-stimulant cohort (n=76). All patients had ADHD impairment rating score (ADHD-IRS) ≥3. Mean change in ADHD-IRS from baseline to day 28 was the primary outcome. A 28-day treatment during STARS-ADHD led to statistically significant improvement in TOVA-API for the trial participants with a positive TOVA-API score 0.9 points higher in the treatment arm versus digital control (p=0.0060). STARS-ADJUNCT trial measured ADHD-IRS mean change from baseline to day 28, which reported a reduction of −0.7 (95% CI, −0.86, −0.50; p <0.001) in the on-stimulant cohort, and −0.5 (95% CI, −0.73, −0.32; p <0.001) in the non-stimulant cohort.

XIV. During STARS-ADJUNCT, exploratory secondary outcomes at day 84 (after a 28-day treatment pause), reported incremental improvement in ADHD-IRS (68.3%), ≥30% improvement in ADHD-RS (45.3%), and CGI-I scores ≤2 (27.6%) across both cohorts. Investigator-monitored compliance

rates were 83% and 81% for STARS-ADHD and STARS-ADJUNCT trials, respectively. Additionally, both clinical trials reported patient-reported improvement in attention deficit (75%).

XV. Limitations of the clinical program for EndeavorRx include a narrow population age, exclusion of patients with psychiatric comorbidities, and short duration of intervention. However, both clinical trials reported consistent, statistically significant improvement in ADHD-related impairment and symptoms of inattention. TOVA-API is a validated tool of improvement in attention deficit and inhibitory control. Clinically meaningful improvements after three months therapy during STARS-ADJUNCT trial (ADHD-RS and CGI-I scores) provide additional indicators of efficacy. For the majority of pediatric patients with ADHD, when used as an adjunct therapy, EndeavorRx may serve as a practical intervention. Overall quality of evidence is considered low to moderate.

XVI. Overall, 12 (7%) and 37 (18%) participants experienced intervention-related adverse reactions (IRAEs) during STARS-ADHD and STARS-ADJUNCT, respectively. During STARS-ADHD, the most common IRAEs between the intervention versus digital control arms respectively, were decreased frustration tolerance (3% vs 0%), headache (2% vs 1%), and irritability (1% in each arm). For STARS-ADJUNCT, IRAEs were evenly distributed between the on-stimulants and non-stimulants cohorts, and included decreased frustration tolerance (13%), irritability (1.5%), headache (1.9%), and dizziness (1%). There were no serious adverse reactions reported. Three participants discontinued STARS-ADJUNCT due to IRAEs. Current safety data for EndeavorRx is limited to the clinical trial population and the real-world long-term safety remains unknown.

Investigational or Not Medically Necessary Uses

I. Somryst and EndeavorRx have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Short-term insomnia
   B. Parasomnia
   C. When used as a stand-alone therapy
   D. Cognitive function improvement in disease conditions other than ADHD (e.g., autism spectrum disorder, systemic lupus erythematosus (SLE))
   E. Sensory processing disorder

II. EndeavorRx has been assessed in clinical trials for pediatric patients with ADHD and comorbid sensory processing disorder (SPD) as well as autism spectrum disorder (ASD). Results of these clinical trials are not available as of June 2023. EndeavorRx has not received FDA-authorization for the above indications.

III. Additional clinical trial to assess the safety and efficacy of EndeavorRx in adolescent population (12 to 17 years of age) with ADHD is ongoing. In June 2023, EndeavorOTC, a non-prescription version of EndeavorRx, became available for use by adults (>18 years of age). EndeavorOTC is available as a downloadable software application (App) compatible with leading cellular phone operating systems and requires a monthly subscription fee. As of June 2023, the results of the clinical trial of EndeavorRx in the adult population are not available. Over-the-counter (OTC) devices and digital therapeutics may be considered excluded in accordance with the benefit designs for this health plan.

References

1. Somryst [Clinician Information]. Boston, MA: Pear Therapeutics, Inc. March 2020.

2. Feuerstein S, Hodges SE, Keenaghan B, Bessette A,Forselius E, Morgan PT. Computerized cognitive behavioral therapy for insomnia in a community health setting. J Clin Sleep Med. 2017;13(2):267-274.
3. Edinger JD, Arnedt JT, Bertisch SM, et al. Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2021;17(2):255–262
4. Kollins SH, DeLoss DJ, Cañadas E, Lutz J, et al.. A novel digital intervention for actively reducing severity of paediatric ADHD (STARS-ADHD): a randomised controlled trial. Lancet Digit Health. 2020 Apr;2(4):e168-e178.
5. Kollins SH, Childress A, Heusser AC, Lutz J. Effectiveness of a digital therapeutic as adjunct to treatment with medication in pediatric ADHD. NPJ Digit Med. 2021 Mar 26;4(1):58.
6. Wolraich M, Brown L, et al. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics. 2011 Nov;128(5):1007-22.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy updated to remove EndeavorRx as a covered benefit	12/2023
Policy created (EndeavorRx) and combined with Somryst to create a Prescription Digital Therapeutics policy.	08/2023

Policy Type: PA/SP Pharmacy Coverage Policy: UMP080

Description
Pretomanid is an orally administered nitroimidazooxazines antimycobacterial agent.

Length of Authorization
- Initial: six months
- Renewal: N/A

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
pretomanid	200 mg tablet	Pulmonary tuberculosis that is extensively drug resistant (XDR), treatment intolerant, or nonresponsive multi-drug resistant (MDR)	30 tablets/30 days	TBD

Initial Evaluation

I. Pretomanid may be considered medically necessary when the following criteria below are met:
   A. The member is 18 years of age or older; **AND**
   B. The medication is prescribed by, or in consultation with a pulmonologist or infectious disease specialist; **AND**
   C. A diagnosis of **pulmonary extensively drug resistant (XDR), treatment-intolerant, or nonresponsive multidrug-resistant (MDR) tuberculosis (TB)** when the following are met:
      1. Documentation of resistance to isoniazid, rifamycins, a fluoroquinolone and an injectable antimicrobial (e.g., amikacin, kanamycin, or capreomycin); **AND**
      2. Documentation of intolerance to para-aminosalicyclic acid (PAS), ethionamide, aminoglycosides or fluoroquinolones; **AND**
      3. The member will be using pretomanid in combination with bedaquiline (Situro) AND linezolid (Zyvox) for the duration of therapy; **AND**
      4. The member will have directly observed treatment (DOT) plan in place

II. Pretomanid is considered investigational when used for all other conditions, including but not limited to:
   A. The use of pretomanid in combination with drugs other than bedaquiline (Situro) and linezolid (Zyvox)
   B. Drug-sensitive (DS) tuberculosis
   C. Latent infection due to Mycobacterium tuberculosis
   D. Extra-pulmonary infection due to Mycobacterium tuberculosis

E. Multidrug-resistant tuberculosis that is not treatment-intolerant or nonresponsive to standard therapy

Supporting Evidence

I. Pretomanid was studied in a Phase 3, open-label trial with 109 adult patients with pulmonary TB that are XDR, treatment intolerant, or non-responsive MDR. In that trial, the safety and efficacy of pretomanid in combination with bedaquline and linezolid was assessed.

Definition of TB Types	
Drug-resistant TB	TB caused by an isolate of Mycobacterium tuberculosis (M. tuberculosis) that is resistant to one or more antituberculous drugs
Multidrug-resistant TB (MDR-TB)	TB caused by an isolate of M. tuberculosis that is resistant to both isoniazid (INH) and rifampin and possibly additional agents
Extensively drug-resistant TB (XDR-TB)	TB caused by an isolate of M. tuberculosis that is resistant to at least INH, rifampin, and fluoroquinolones as well as either aminoglycosides (e.g. amikacin, kanamycin) or capreomycin or both
Totally drug-resistant TB (TDR-TB)	TB caused by an isolate of M. tuberculosis resistant to all locally tested medications

II. The primary efficacy outcome was the incidence of bacteriologic failure, relapse, or clinical failure through follow up until six months after the end of treatment; of the 107 patients assessed, 12 (11%) patients were classified as treatment failure, while 95 (89%) patients were classified as treatment success. Treatment success was defined as culture negative status at six months post treatment.
III. No pediatric patients were included in the trial.
IV. Pretomanid was only studied in combination with bedaquiline (Situro) and linezolid (Zyvox).
V. Patients that were included in the trial demonstrated resistance to isoniazid, rifamycins, a fluroquinolone and an injectable antimicrobial, and had intolerance to para-aminosalicyclic acid (PAS), ethionamide, aminoglycosides or fluoroquinolones.

Investigational or Not Medically Necessary Uses

I. Safety and efficacy has not been established for the use of pretomanid in combination with drugs other than bedaquiline (Situro) and linezolid (Zyvox).
II. Pretomanid was FDA-approved on an accelerated approval pathway under the Limited Population Pathway for Antibacterial and Antifungal Drugs. As stated in the label, the approval of this indication is based on limited clinical safety and efficacy data. Therefore, the use of this drug is indicated for a very specific population of patients, and antimicrobial stewardship practices should be applied when treating this population of patients. Therefore, the use of pretomanid in setting

other than the label indication [pulmonary extensively drug resistant (XDR), treatment-intolerant, or nonresponsive multidrug-resistant (MDR) tuberculosis (TB)], is considered experimental and investigational.

References

1. Pretomanid [Prescribing Information]. Mylan: Hyderabad, India. August 2019.
2. Sirturo [Prescribing information]. Janssen Therapeutics: Titusville,NJ. December 2012.
3. Center for Disease Control and Prevention: Provisional CDC Guidelines for the Use and Safety Monitoring of Bedaquiline Fumarate (Sirturo) for the Treatment of Multidrug-Resistant Tuberculosis. Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6209a1.htm?s_cid=rr6209a1_e
4. World Health Organization: WHO Guidelines on Tuberculosis. Available at: https://www.who.int/news-room/fact-sheets/detail/tuberculosis
5. The Food and Drug Administration: FDA Briefing Document on Pretomanid 200 mg Tablet. Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC). June 2019.
6. Clinicaltrial.gov

Policy Implementation/Update:

Date Created	September 2019
Date Effective	November 2019
Last Updated	
Last Reviewed	

Action and Summary of Changes	**Date**

Policy Type: PA/SP Pharmacy Coverage Policy: UMP001

Description
Alirocumab (Praluent) and evolocumab (Repatha) are subcutaneous Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) inhibitors.

Length of Authorization
- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
alirocumab (Praluent)	75 mg/mL pen injector	Heterozygous familial hypercholesterolemia; Homozygous familial hypercholesterolemia; Atherosclerotic cardiovascular disease; Non-familial hypercholesterolemia	2 mL (2 injections)/28 days
	150 mg/mL pen injector		
evolocumab (Repatha)	140 mg/mL auto injector; prefilled syringe		2 mL (2 injections)/28 days
	420 mg/mL solution cartridge		3.5 mL (1 injection)/28 days

Initial Evaluation

I. **Alirocumab (Praluent) or evolocumab (Repatha)** may be considered medically necessary when the following criteria below are met:
   A. Therapy is prescribed by, or in consultation with, a provider specializing in lipid management (e.g., cardiology, lipidology, endocrinology); **AND**
   B. The member has an LDL-C level greater than, or equal to, 70 mg/dL while on maximally tolerated statin therapy; **AND**
   C. If the request is for alirocumab (Praluent), treatment with evolocumab (Repatha) has been ineffective, not tolerated, or contraindicated; **AND**
   D. Therapy with a high intensity statin (greater than, or equal to, atorvastatin [Lipitor] 40 mg or rosuvastatin [Crestor] 20 mg) for at least an 8-week duration has been ineffective; **AND**
      1. The member will continue statin therapy in combination with alirocumab (Praluent) or evolocumab (Repatha); **OR**
   E. Provider attestation that there is clinical documentation of statin failure defined by <u>one</u> of the following:
      1. Treatment with maximally tolerated doses of any statin (e.g., simvastatin [Zocor], pravastatin [Pravachol], etc.) was ineffective or contraindicated; **OR**

2. The member has not tolerated at least two statin medications as defined by at least one of the following:
    i. CK exceeds 10 times the upper limit of normal
    ii. LFTs exceed 3 times the upper limit of normal
    iii. Severe muscle weakness inhibiting activities of daily living, employment, or leading to temporary disability; **OR**
3. The member experienced severe rhabdomyolysis after the use of at least one statin; **AND**

F. A diagnosis of one of the following:
1. **Atherosclerotic cardiovascular disease (ASCVD); AND**
    i. Member is 18 years of age or older; **AND**
    ii. Attestation that there is clinical documentation supporting a diagnosis clinical atherosclerotic disease via invasive or non- invasive testing (e.g., stress test, imaging); **OR**
    iii. Diagnosis of atherosclerotic disease and primary prevention failure (e.g., member has had a stroke, myocardial infarction); **OR**
2. **Heterozygous familial hypercholesterolemia**; **AND**
    i. The member is 18 years of age or older; **OR**
        a. The member is 10 years of age or older and the request is for evolocumab (Repatha); **AND**
    ii. Diagnosis of heterozygous familial hypercholesterolemia is confirmed by one of the following
        a. Genotyping or clinical criteria using either the Simon Broome diagnostic criteria (definite diagnosis classification) or Dutch Lipid Network criteria (score greater than 8)
        b. Attestation that there is clinical documentation or a DNA mutation analysis supporting the diagnosis of heterozygous familial hypercholesterolemia; **OR**
3. **Homozygous familial hypercholesterolemia**; **AND**
    i. The member is 18 years of age or older; **OR**
        a. The member is 10 years of age or older and the request is for evolocumab (Repatha); **AND**
    ii. The member has a history of an untreated LDL-cholesterol level greater than 500 mg/dL with either evidence of heterozygous familial hypercholesterolemia in both parents or xanthoma before the age of 10; **OR**
        a. Attestation that there is documentation of DNA mutation analysis supporting the diagnosis of homozygous familial hypercholesterolemia (e.g, *LDLR, APOB, PSCK9, LDLRAP1*); **AND**
    iii. Evolocumab (Repatha) or alirocumab (Praluent) will not be used in combination with lopitamide (Juxtapid)
4. **Non-familial hypercholesterolemia; AND**
    i. The member is 18 years of age or older; **AND**

ii. The member has a history of an untreated LDL-C level greater than, or equal to, 190 mg/dL; **AND**
iii. Treatment with ezetimibe (Zetia) has been ineffective, contraindicated, or not tolerated; **AND**
iv. The member is unable to achieve ≥50% LDL-C reduction and LDL-C <100 mg/dL or non-HDL-C <130 mg/dL on maximally tolerated cholesterol lowering therapy; **AND**
v. Provider attestation hypercholesterolemia is not due to a reversible/untreated secondary cause (e.g. hypothyroidism, nephrotic syndrome, primary biliary cholangitis)

II. Alirocumab (Praluent) or evolocumab (Repatha) are considered investigational when used for all other conditions, including but not limited to:
A. ASCVD primary prevention in non-familial hypercholesterolemia with untreated LDL-C < 190 mg/dL

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has experienced a decrease from baseline LDL-C while on therapy; **AND**
IV. If the request is for alirocumab (Praluent), treatment with evolocumab (Repatha) has been ineffective, not tolerated, or contraindicated

Supporting Evidence

I. Alirocumab (Praluent) is FDA-approved to reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease and 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) or homozygous familial hypercholesterolemia who require additional lowering of low-density lipoprotein cholesterol (LDL-C).
II. Evolocumab (Repatha) is FDA-approved to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease and as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of patients 10 years and older with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) or homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

III. The 2017 American Association of Clinical Endocrinologists (AACE) guidelines state statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials. Additionally, guidelines state PCSK9 inhibitors should be considered in individuals with clinical cardiovascular disease who are unable to reach LDL-C/non-HDL-C goals with maximally tolerated statin therapy. They should not be used as monotherapy except in statin-intolerant individuals.

IV. Seventy to ninety percent of patients are able to tolerate an alternate long-term statin. In clinical practice, 10-25% of patients have musculoskeletal adverse events associated with statin use; however, several studies have determined that the majority of patients with statin-associated muscle symptoms are able to tolerate subsequent statin therapy with modified dosing regimens.

V. The 2011 National Lipid Association (NLA) familial hypercholesterolemia guidelines define ineffective therapy as inability to achieve an LDL-C of less than 70 mg/dL with treatment in atherosclerotic cardiovascular disease.

VI. **Atherosclerotic cardiovascular disease (ASCVD)**: 2018 American Heart Association/American College of Cardiology (AHA/ACC) Cholesterol Guidelines recommend patients with clinical ASCVD reduce LDL-C with high-intensity statin therapy or maximally tolerated statin therapy. In patients with clinical ASCVD who are judged to be very high risk and considered for PCSK9 inhibitor therapy, maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe (very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions).

- The 2017 American College of Cardiology (ACC) Recommendations for Non-Statin Therapy recommends consideration of adding ezetimibe first in patients that are statin intolerant with clinical ASCVD and may consider a bile acid sequestrant as an alternative if ezetimibe intolerant and triglycerides <300 mg/dL.
- Ezetimibe is a clinically appropriate and cost-effective alternative to PSCK9 inhibitors in scenarios where addition of ezetimibe would be expected to bring LDL-C levels to a patient specific LDL-C goal. In patients with ASCVD, the 2018 AHA/ACC Cholesterol Guidelines recommend achieving a ≥50% reduction in LDL-C levels and an LDL-C goal of <70mg/dL. The 2021 European Society of Cardiology Guidelines recommend lipid-lowering treatment with an ultimate goal of <55mg/dL and a ≥50% reduction of LDL-C from baseline. Depending on specific risk factors, providers may choose different LDL-C goals for their patients. Ezetimibe is cited to lower LDL-C by 15-20% when used by itself or in combination with a statin. Therefore, information about patient's specific LDL-C goals and concomitant cholesterol lowering therapies is required to estimate overall LDL-C lowering effect and assess appropriateness of treatment with ezetimibe.
- Per Schmidt et al. Cochrane Review, "In comparisons of PCSK9 inhibitors versus no PCSK9 inhibitors, current evidence suggests that PCSK9 inhibitors decrease CVD incidence without affecting the incidence of all-cause mortality. In comparisons of PCSK9 inhibitors versus alternative (more established) treatments such as statins or ezetimibe, high-quality evidence is lacking. Differences in risk between people treated with and without PCKS9 inhibitors suggest the absolute treatment benefit will likely be modest (e.g., < 1% change in risk)."

VII. Insight from cardiology specialists indicate that diagnosis of clinical ASCVD in the absence of a cardiovascular event can be achieved by angiography, ischemia on stress test, or stenosis of 50% or more using other imaging techniques. While evidence of coronary calcification on CTA (calcium score >1) is indicative of high-risk of developing ASCVD, this number should be integrated into the member's clinical profile to determine individual patient risk and treatment but should not necessarily be used alone for the purposes of clinical diagnosis.

VIII. **Heterozygous familial hypercholesterolemia**: The presence of tendon xanthoma is a genetically modulated clinical syndrome of familial hypercholesterolemia. In addition, DNA testing can be used to diagnose familial hypercholesterolemia functional mutations. In clinical trials, enrolled patients with heterozygous familial hypercholesterolemia were diagnosed either by genotyping or clinical criteria ("definite FH" using either the Simon Broome or Dutch Lipid Network).

Simon Broome Familial Hypercholesterolemia Register diagnostic criteria for familial hypercholesterolemia	
Criteria	**Description**
A	Total cholesterol concentration above 7.5 mmol/liter (290 mg/dL) in adults or a total cholesterol concentration above 6.7 mmol/liter (259 mg/dL) in children aged less than 16 years, or
	Low density lipoprotein cholesterol concentration above 4.9 mmol/liter (189 mg/dL) in adults or above 4.0 mmol/liter (155 mg/dL) in children
B	Tendinous xanthomata in the patient or a first-degree relative
C	DNA-based evidence of mutation in the *LDLR, PCSK9,* or *APOB* gene
D	Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative
E	Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative
A "definite" FH diagnosis requires either criteria a and b, or criterion c. A "probable" FH diagnosis requires either criteria a and d, or criteria a and e.	

Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia	
Criteria	**Points**
Family history	
• First-degree relative with known premature (men: <55 years; women: <60 years) coronary or vascular disease, or • First-degree relative with known LDL-C above the 95th percentile	1
• First-degree relative with tendinous xanthomata and/or arcus cornealis, or • Children <18 years of age with LDL-C above the 95th percentile	2
Clinical History	
• Patient with premature (men: <55 years; women: <60 years) coronary artery disease	2
• Patient with premature (men: <55 years; women: <60 years) cerebral or peripheral vascular disease	1
Physical examination	
• Tendinous xanthomata	6

• Arcus cornealis before age 45 years	4
LDL-C levels	
• LDL-C ≥8.5 mmol/L (325 mg/dL)	8
• LDL-C 6.5-8.4 mmol/L (251-325 mg/dL)	5
• LDL-C 5.0-6.4 mmol/L (190-250 mg/dL)	3
• LDL-C 4.0-4.9 mmol/L (155-189 mg/dL)	1
DNA analysis	
• Functional mutation in the LDLR, apoB, or PCSK9 gene	8
Choose only one score per group, the highest applicable diagnosis (diagnosis is based on the total number of points obtained) • A "definite" FH diagnosis requires >8 points • A "probable" FH diagnosis requires 6-8 points • A "possible" FH diagnosis requires 3-5 points	

- Using DNA testing, patients with familial hypercholesterolemia (FH) have been identified as generally having a functional mutation of one of three genes: *LDLR, PCSK9,* or *APOB* gene. Mutations in these three genes can be detected in about 80 percent of patients with the definite FH clinical syndrome.
- The 2017 AACE guidelines state PCSK9 inhibitors should be considered for use in combination with statin therapy for LDL-C lowering in individuals with FH.

IX. **Homozygous familial hypercholesterolemia (HoFH):** Evolocumab (Repatha) and alirocumab (Praluent) are FDA-approved in the setting of HoFH and includes patients ages 13 and older (Repatha) or 18 and older (Praluent). Evocolumab (Repatha) was studied in one multi-center, double-blind, randomized, placebo-controlled trial (TESLA Part B) in patients greater than, or equal to, 13 years of age with homozygous familial hypercholesterolemia. Patients in the clinical trial had familial hypercholesterolemia diagnosed either by genetic analysis or clinical criteria (history of an untreated LDL cholesterol concentration >13 mmol/L (500 mg/dL)) plus either xanthoma before 10 years of age or evidence of heterozygous familial hypercholesterolemia in both parents. Alirocumab (Praluent) was studied in one randomized, double-blind, placebo-controlled, parallel-group, phase 3 study (ODYSSEY HoFH) in patients 18 years of age or older with homozygous familial hypercholesterolemia. Patients in the clinical trial had a diagnosis of familial hypercholesterolemia confirmed in the patient's medical history by clinical diagnosis or by genotyping. The genotyping results from this study found patients had mutations in the *LDLR, LDLRAP1, PCSKP,* or *APOB* genes.

- Use of evolocumab (Repatha) and alirocumab (Praluent) with mipomersen (Kynamro) or lopitamide (Juxtapid) has not been studied in a large population, and the efficacy and safety is unknown. Concurrent use is considered experimental and investigational.

X. **Non-familial hypercholesterolemia**

- The use of statins, including in patients considered to be high risk, is recommended as first line therapy by multiple guidelines. Statins have pleiotropic effects, which involves improvement of endothelial function, decreasing oxidative stress and inflammation, enhancing stability of atherosclerotic plaques, and inhibiting thrombogenic response. These pleiotropic effects have been hypothesized for PCSK9 inhibitors in preclinical studies but have not yet been established.

- Long term risk of ASCVD or CHD (defined as CHD death or non-fatal MI) in adults with familial hypercholesterolemia phenotype (defined as LDL-C levels ≥ 190 mg/dL, irrespective of genetic confirmation of true familial hyperlipidemia or family history of cardiovascular disease) was evaluated using pooled data from 6 large epidemiological studies consisting of 68,565 patients between 20 and 79 years old. The reference group were patients with LDL-C <130 mg/dL. Sensitivity analyses were utilized for patients with LDL-C levels ≥ 190 mg/dL and positive family history. Statin or other hyperlipidemia medications were not specifically reported out within the trial, but it was noted that the vast majority of the data were collected before widespread use of statins. Rate of cholesterol treatment at baseline were very low, between 0% and 4.4% for the different analysis arms, with slightly higher but statistically significant usage within the ≥ 190 mg/dL population for certain age groups. Baseline characteristics were largely the same, but there were statistically significant higher proportion of smokers and hypertension treatment at baseline in the LDL ≥ 190 mg/dL. Overall, adjusted for age, race, BMI, DM, smoking, blood pressure treatment, patients with LDL ≥ 190 mg/dL were at 1.3 (95% CI 1.0-1.7) to 5.0 (95% CI 1.1-21.7) times higher risk of CHD and up to 4.1x higher total risk of ASCVD (HR 4.1 (95% CI, 1.2-13.4). Hazard ratios for CHD risk decreased with age but was significant in all age groups except those between 70-79 years old (HR 1.3; 95% CI 1.3 (1.0-1.7)). This study demonstrated that irrespective of genetic confirmation of familial hyperlipidemia or family history of cardiovascular disease, patients with LDL-C levels ≥ 190 mg/dL, were at 2-5x higher risk of CHD, and up to 4x higher risk for ASCVD.
- Khera et al. assessed the relationship between severe hypercholesterolemia (defined as untreated LDL-C ≥190 mg/dl) and CAD risks, found that among 20,485 CAD-free and prospective cohort participants, 1,386 (6.7%) had LDL ≥ 190 mg/dL, and of those, gene sequencing only identified 24 patients (1.7%) with FH mutation. Compared to reference group of LDL <130 mg/dl and no mutation, those with LDL ≥190 mg/dL and had no FH mutation were at 6x higher risk for CAD (OR 6.0; 95% CI 5.2-6.9), and those with ≥190 mg/dL and FH mutation were at 22x higher risk (OR 22.3; 95% CI (10.7-53.2)). This data suggests that even patients without confirmed genetic familial hypercholesterolemia but severe untreated LDL-C ≥ 190 mg/dL are at significantly higher risk of developing CAD.
- A systematic review and meta-analysis containing a total of 312,175 patients from 49 trials among different therapeutic interventions demonstrated a relative risk for major vascular events per 1-mmol/L (38.7 mg/dL) reduction in LDL-c level was 0.77 (95% CI, 0.71-0.84; p<0.001) for statins and 0.75 (95% CI, 0.66-0.86; P=0.002) for non-statin therapies. The meta-analysis consisted of trials assessing statins (25), ezetimibe (1), fibrates (9), niacin (3), CETP inhibitors (3), diet (4), bile acid sequestrants (2), ileal bypass (1), and PCSK9-inhibiotrs (2). Primary prevention trials achieved 1.5% (95% CI, 0.5%-2.6%) lower event rate of major coronary events per each 38.7 mg/dL LDL-C level reduction (p=0.008) and secondary prevention trials achieved 4.6% (95% CI, 2.9%-6.4%) lower event rate per 38.7 mg/dL LDL-C level reduction (p<0.001). Major vascular events included: cardiovascular death, acute MI

or other ACS, coronary revascularization, or stroke. The two PCSK9 inhibitor studies (ODYSSEY Long Term and OSLER) consisted of 6,808 patients and demonstrated a 0.49 relative risk (95% CI, 0.34-0.71) between treatment and control groups for each 38.7 mg/dL reduction in LDL. ODYSSEY and OSLER contained both primary and secondary prevention patients. In conjunction with evidence that PCSK-9 inhibitors

- OSLER-1 and OSLER-2 were longer-term Open-Label extension trials for five Phase 2 (MENDEL-1, LAPLACE-TIMI 57, GAUSS-1, RUTHERFORD-1, YUKAWA-1) and seven Phase 3 trials (MENDEL-2, LAPLACE-2, GAUSS-2, RUTHERFORD-2, DECSCARTES, THOMAS-1, THOMAS-2) evaluating evolocumab. OSLER demonstrated a 1.23% absolute risk reduction of cardiovascular events (i.e. death, MI, unstable angina requiring hospitalization, coronary revascularization, stroke, transient ischemic attack, heart failure hospitalization) between evolocumab plus standard of care group vs standard of care alone group at 1 year (0.95% vs 2.18%, respectively). With regards to LDL-C lowering, evolocumab demonstrated greater than 70 mg/dL absolute reduction in LDL-C by 12 weeks, and approximately a 60% reduction in LDL-C. This reduction in LDL-C was sustained at every time point through 48 weeks. About 10% of patients enrolled in OSLER had known familial hypercholesterolemia, 20% had coronary artery disease, 24% had family history of premature coronary artery disease, and 9% had cerebrovascular or peripheral artery disease. The patient characteristics of these trials demonstrate that statistically significant absolute risk reduction of cardiovascular events can be achieved even when the majority of patients did not have familial hypercholesterolemia or coronary artery disease at baseline.
- The DESCARTES trial, a 52-week randomized placebo-controlled trial containing 901 adult patients between 18 and 75 years old with LDL cholesterol of ≥75mg/dL and fasting triglyceride of ≤400 mg/dL. After a 4-week run-in period, patients with CHD or CHD risk equivalent and LDL < 100 mg/dL, or no CHD or CHD risk equivalent and LDL <130 mg/dL, or on maximal background therapy were randomized 2:1 to evolocumab 420mg SC Q4W or Placebo between 4 different treatment arms; patients treated with diet alone, patients treated with diet and atorvastatin 10 mg, patients treated with diet and atorvastatin 80mg, and patients treated with diet, atorvastatin 80mg and ezetimibe 10mg. At baseline, 15.1% of patients had coronary artery disease, but prevalence of familial hyperlipidemia was not reported. Given the mean baseline LDL-C was between 94.6 to 119.8 mg/dL, the proportion of patients with familial hyperlipidemia is expected to be relatively low compared to the overall study population. Overall, the DESCARTES study demonstrated a statistically significant -57.0% ± 2.1% mean change from baseline in LDL between evolocumab and placebo group at 52 weeks. 82.3% of patients achieved LDL of <70 mg/dL at 52 weeks, compared to 6.5% for the placebo group. Roughly 1/3rd of the patients that achieved LDL <70mg/dL while on placebo at 52 weeks were from the diet plus 80mg atorvastatin plus ezetimibe 10mg arm. Within this treatment arm, there was a -48.5± 5.2 mean difference in percent change from baseline LDL cholesterol at 52 weeks of treatment. The DESCARTES trial demonstrated that even while on max dose high intensity statin and ezetimibe, the addition of a PCSK9-

inhibitor can still achieve significant reduction in LDL cholesterol levels from baseline.

- Per 2022 ACC Expert Consensus Decision Pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk, there is a pathway for consideration of PCSK9 inhibitors for adults without clinical ASCVD and with baseline LDL-C ≥190 mg/dL not due to secondary causes who are taking statin therapy for primary prevention. The panel recommends the addition of ezetimibe and/or PCSK9 inhibitors to maximally tolerated statin therapy if LDL-C reduction of ≥50% LDL-C reduction and LDL-C <100 mg/dL or non-HDL-C <130 mg/dL is not achieved.
- Secondary causes of hypercholesterolemia are caused by medications, substances, and medical conditions leading to elevated levels of LDL and other lipids. Hypothyroidism, nephrotic syndrome, primary biliary cholangitis, and diabetes have the most supporting evidence to suggest a link between the condition and secondary elevation of lipid levels, specifically LDL cholesterol. In line with the recommendations from the 2018 ACC/AHA guidelines and 2022 ACC Expert Consensus recommendations, LDL elevation due to secondary causes does not warrant the same level of consideration for treatment with the exception of diabetes. Although diabetes is an established secondary cause of hypercholesterolemia, the condition is also a significant risk factor that warrants additional and more intensive lipid lowering to reduce the risk of atherosclerosis.
- Safety and efficacy of PCSK9 inhibitors, specifically Repatha (evolocumab) has not been established in non-familial hyperlipidemia pediatric patients.

Investigational or Not Medically Necessary Uses

I. ASCVD Primary prevention non-familial hypercholesterolemia with LDL-C < 190 mg/dL
   A. Currently, there is no established data to support the use of PCSK-9 inhibitors in the primary prevention setting for patients with an LDL-C level below 190 mg/dL. In accordance with the 2022 ACC Expert Consensus statement and 2023 American Diabetes Association Standards of Care in Diabetes Guidelines, in the absence of ASCVD or baseline LDL-C 190 mg/dL, PCSK-9 inhibitors do not have an established, evidence-based role for primary prevention of ASCVD. For patients without ASCVD and have and LDL-C of 70-189 mg/dL, the ACC Expert writing committee does not routinely recommend PCSK9 inhibitors given limited efficacy data and low cost-effectiveness in primary prevention patients on statin therapy.
   B. According the 2018 AHA/ACC clinical guidelines, patients with an LDL-C of ≥ 190 mg/dL in primary prevention or secondary prevention are at a higher risk of future ASCVD events, and do not require a risk assessment before starting lipid lowering therapy. Patients with a baseline LDL-C between 70 mg/dL and 189 mg/dL are at lower risk of future ASCVD events, and ASCVD risk assessment is warranted before initiation of therapy. The use of statin is recommended as the first line treatment option for these patients.
   C. Within the 2022 ACC Expert Consensus statement, an LDL-C cutoff of 190 mg/dL is utilized direct management to PCSK9 inhibitors. For adults with possible statin intolerance without

clinical ASCVD and LDL-C <190 mg/dL, ezetimibe is considered the first line non-statin therapy, and bile acid sequestrants are considered second-line therapy. PCSK9 inhibitors are not included in this recommendation pathway unless than member has clinical ASCVD or an LDL-C > 190mg/dL. Standard LDL-C scales and lipid panels considers an LDL of 160-189 mg/dL as high, and LDL of ≥ 190 mg/dL as very high or severely elevated. An LDL of 160-189 mg/dL in primary hypercholesterolemia is considered a risk-enhancing factor for clinician-patient risk discussion.

A 14,570-participant cohort study presented at the American Heart Association 2021 Scientific Sessions compared the risk of major adverse cardiovascular events (MACE) in the next 10 years in patients between 20-39 years old with an LDL-C of 160-189 mg/dL to patients with an LDL-C of less than 160 mg/dL. Results showed that the risk of MACE were not significantly different between the two groups (OR. 1.28 [95% CI, 0.94-1.74; p <0.115). MACE was defined as all-cause death, MI, ischemic stroke, heart failure hospitalization, and peripheral vascular disease. While there was not a comparison cohort of patients with LDL-C > 190mg/dL in this study, the result is in line with the understanding that patients with an LDL-C of <190 mg/dL are not at a significantly higher risk for ASCVD and major adverse cardiovascular events, even if their LDL-C is elevated at 160-189 mg/dL.

References

1. Jacobson T, Ito M, Maki K, et al. National Lipid Association recommendations for patient- centered management of dyslipidemia: Executive Summary. J Clin Lipidol. 2014;8(5):473– 488.
2. Stroes E, Colquhoun D, Sullivan D, et al. Anti-PCSK9 Antibody Effectively Lowers Cholesterol in Patients With Statin Intolerance (GAUSS-2). J Am Coll Cardiol 2014; 63:2541-8
3. Raal FJ, Honarpour N, Blom DJ, et al. Inhibition of PCSK9 with Evolocumab (Repatha) in homozygous familial hypercholesterolaemia (TESLA Part B). Lancet 2015; 385: 341–50
4. Raal FJ, Stein EA, Dufour R, et al. PCSK9 inhibition with Evolocumab (Repatha) (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2). Lancet 2015; 385: 331– 40
5. Stone N, Robinson J, Lichtenstein AH et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129(25 Suppl.2):S1–S45.
6. Robinson JG, Farnier M, Krempf M, et al for the ODYSSEY LONG TERM Investigators. Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events. N Engl J Med 2015;372:1489-1499.
7. Praluent. Package Insert. Sanofi-Aventis U.S. LLC; 2021.
8. Repatha. Package Insert. Amgen, Inc; 2021.
9. Koren MJ, Lundqvist P, Bolognese M, et al. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol. 2014;63(23):2531-40.
10. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017; 376(18):1713-1722
11. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines For Management of Dyslipidemia and Prevention of Cardiovascular Disease - Executive Summary. Endocr Pract. 2017;23(4):479-497.
12. Uptodate, Inc, Familial hypercholesterolemia in adults: Overview. UpToDate [database online]. Waltham, MA. Updated 04/15/2019. Available at: http://www.uptodate.com/home/index.html.
13. Lloyd-jones DM, Morris PB, Ballantyne CM, et al. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2017;70(14):1785-1822.

14. Schmidt AF, Pearce LS, Wilkins JT, Overington JP, Hingorani AD, Casas JP. PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2017;4:CD011748.
15. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;
16. Blom DJ et al. Efficacy and Safety of Alirocumab in Adults with Homozygous Familial Hypercholesterolemia: The ODYSSEY HoFH Trial. J A Coll Cardiol 2020;76:131-42
17. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227-3337. doi:10.1093/eurheartj/ehab484
18. Lloyd-Jones D, Morris P, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. *J Am Coll Cardiol.* 2022 Oct, 80 (14) 1366–1418.
19. Blom DJ, Hala T, Bolognese M, et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *N Engl J Med*. 2014;370(19):1809-1819.
20. Silverman MG, Ference BA, Im K, et al. Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions: A Systematic Review and Meta-analysis. *JAMA.* 2016;316(12):1289–1297. doi:10.1001/jama.2016.13985
21. Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372(16):1500-1509. doi:10.1056/NEJMoa1500858
22. Vodnala D, Rubenfire M, Brook RD. Secondary causes of dyslipidemia. *The American Journal of Cardiology*. 2012;110(6):823-825. doi:10.1016/j.amjcard.2012.04.062
23. Perak AM, Ning H, de Ferranti SD, Gooding HC, Wilkins JT, Lloyd-Jones DM. Long-term risk of atherosclerotic cardiovascular disease in US adults with the familial hypercholesterolemia phenotype. *Circulation*. 2016;134(1):9-19. doi:10.1161/circulationaha.116.022335
24. Lamiquiz-Moneo I, Civeira F, Mateo-Gallego R, et al. Diagnostic yield of sequencing familial hypercholesterolemia genes in individuals with primary hypercholesterolemia. *Revista Española de Cardiología (English Edition)*. 2021;74(8):664-673. doi:10.1016/j.rec.2020.06.003
25. Wiegman A, Gidding SS, Watts GF, et al. Familial hypercholesterolaemia in children and adolescents: Gaining decades of life by optimizing detection and treatment. *European Heart Journal*. 2015;36(36):2425-2437. doi:10.1093/eurheartj/ehv157
26. Yanai H, Yoshida H. Secondary Dyslipidemia: Its treatments and association with atherosclerosis. *Global Health & Medicine*. 2021;3(1):15-23. doi:10.35772/ghm.2020.01078
27. ElSayed NA, Aleppo G, Aroda VR, et al., American Diabetes Association. Summary of revisions: *Standards of Care in Diabetes—2023*. Diabetes Care 2023;46(Suppl. 1):S5–S9
28. Lee Y, Siddiqui WJ. Cholesterol Levels. PubMed. Published 2020. Available at: https://www.ncbi.nlm.nih.gov/books/NBK542294/#:~:text=LDL%2DC%20level%3A
29. Campbell P. LDL-C Above 160 mg/dL Associated with Increased MACE Risk in Younger Patients. Practical Cardiology. Updated 11/15/2021. Available at: https://www.practicalcardiology.com/view/ldl-c-above-160-mg-dl-associated-with-increased-mace-risk-in-younger-patients

Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of non-familial hypercholesterolemia criteria and supporting evidence. Removed not medically necessary criteria for Hypercholesterolemia non-familial cause indication, and added ASCVD primary prevention non-familial hypercholesterolemia with LDL-C 190mg/dl to experimental and investigational criteria. Minor formatting changes.	02/2023
Updated to allow provider attestation in HoFH DNA mutation analysis. Require history with only one statin in the setting of previous rhabdomyolysis.	01/2023
Removed ezetimibe step criteria for ASCVD. Included trial of Repatha prior to Praluent within renewal criteria.	12/2022
Added criteria allowing a path to coverage in scenarios where ezetimibe would not be expected to bring LDL-C levels to a desired LDL-C goal. Updated supporting evidence.	08/2022
Updated to include age expansion in pediatric patients aged 10 years and older with heterozygous familial hypercholesterolemia (HeFH) or homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C	02/2022

Added new FDA-approved indication of HoFH for Praluent. Updated diagnosis confirmation requirements for HeFH and HoFH to align with current guidelines. Removed statement around combination use with Kynamro as product has been discontinued. Update to supporting evidence.	04/2021
Review. Update to supporting evidence	12/2020
Updated to policy format. Added requirement of ezetimibe trial and failure in ASCVD.	06/2019
Addition of Repatha 420mg/3.5mL pushtronex system to the approval language.	11/2018
Removed alternate statin dosing strategies in patients who are statin intolerant. Decreased LDL cutoff to >70 for all indications. Increased initial authorization to 12 months. Removed requirement to try and fail statin plus Zetia combination therapy. Removed DNA mutation analysis confirming homozygous familial hypercholesterolemia diagnosis. Required trial and failure of high intensity statin for a minimum of 8 week duration. Updated renewal criteria to assess overall reduction in LDL rather than specific percent reduction.	06/2018
Previous review	11/2017
Removed triple step therapy with an additional LDL lowering agent. Increased initial authorization to 6 months.	02/2016
Criteria created	08/2015

Policy Type: PA/SP Pharmacy Coverage Policy: UMP145

Description

Ambrisentan (generic, Letairis®), bosentan (generic, Tracleer®), and macitentan (Opsumit®) are endothelin receptor agonists (ERA) that inhibit the binding of endothelin – a vasoconstrictive peptide – to its receptors (ET_A and ET_B) in the endothelium and smooth muscle cells which results in vasodilation.

Riociguat (Adempas®) stimulates soluble guanylate cyclase (sGC) – a receptor for nitric oxide and an enzyme in the cardiopulmonary system. It sensitizes sGC to endogenous nitric oxide by stabilizing nitric oxide-sGC binding and directly stimulating sGC via a different binding site. Stimulating the nitric oxide-sGC-cGMP pathway, leads to an increased generation of cGMP and subsequent vasodilation.

Iloprost (Ventavis®) inhalation solution, treprostinil (Tyvaso®) inhalation solution, treprostinil (Orenitram®) tablets for oral use, treprostinil (Remodulin®) injection for subcutaneous use and selexipag (Uptravi®) tablets for oral use are prostacyclin vasodilators. They directly vasodilate pulmonary and systemic arterial vascular beds, inhibit platelet aggregation, and inhibit smooth muscle cell proliferation.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
ambrisentan (Letairis)	Pulmonary arterial hypertension (PAH)	5 mg tablets	30 tablets/30 days
		10 mg tablets	
generic ambrisentan		5 mg tablets	30 tablets/30 days
		10 mg tablets	
bosentan (Tracleer)		32 mg tablet for oral suspension	120 tablets/30 days
		62.5 mg film-coated tablet	60 tablets/30 days
		125 mg film-coated tablet	
generic bosentan		32 mg tablet for oral suspension	120 tablets/30 days
		62.5 mg film-coated tablet	60 tablets/30 days
		125 mg film-coated tablet	
macitentan (Opsumit)		10 mg tablet	30 tablets/30 days
riociguat (Adempas)	Chronic thromboembolic pulmonary	0.5 mg tablets	90 tablets/30 days
		1 mg tablets	
		1.5 mg tablets	

	hypertension (CTEPH); Pulmonary arterial hypertension (PAH)	2 mg tablets	
		2.5 mg tablets	
iloprost (Ventavis)	Pulmonary arterial hypertension (PAH)	10 mcg/mL inhalation solution ampule	9 cartons of 30 ampules per 30 day supply
		20 mcg/mL inhalation solution ampule	
treprostinil (Tyvaso)	Pulmonary arterial hypertension (PAH); Pulmonary hypertension (PH) Due to Interstitial Lung Disease (ILD)	1.74 mg/2.9 mL inhalation solution ampule	1 Inhalation System Starter Kit (28 ampule carton)/ 1st 28 days of initiation therapy 1 Inhalation System Refill Kit (28 ampule carton)/28 days 7 Four Pack Cartons with one foil pouch containing four 2.9 mL ampules/28 days
treprostinil (Tyvaso DPI)		Maintenance Kit 16 mcg cartridge	112 cartridges/28 days
		Maintenance Kit 32 mcg cartridge	
		Maintenance Kit 48 mcg cartridge	
		Maintenance Kit 64 mcg cartridge	
		Maintenance Kit 32 mcg & 48 mcg	224 cartridges/28 days
		Titration Kit 16 mcg & 32 mcg	196 cartridges/28 days
		Titration Kit 16 & 32 & 48 mcg	252 cartridges/28 days
treprostinil (Remodulin)	Pulmonary arterial hypertension (PAH)	5 mg/mL injection solution	up to 50 ng per kg per minute subcutaneously or intravenously
		10 mg/mL injection solution	
		20 mg/20 mL injection solution	
		50 mg/20 mL injection solution	
		100 mg/20 mL injection solution	
		200 mg/20 mL injection solution	
treprostinil (Orenitram)		0.125 mg ER tablet	90 extended-release oral tablets/30 days
		0.25 mg ER tablet	

		1 mg ER tablet	
		2.5 mg ER tablet	
		5 mg ER tablet	
selexipag (Uptravi)		200 mcg	140 oral use tablets/28 days
		400 mcg	Titration pack (140 count – 200mcg oral use tablets + 60 count – 800mcg) 60 oral use tablets/30 days
		600 mcg	
		800 mcg	
		1000 mcg	
		1200 mcg	
		1400 mcg	
		1600 mcg	

Initial Evaluation

I. **Ambrisentan (Letairis), generic ambrisentan, bosentan (Tracleer), generic bosentan, macitentan (Opsumit), riociguat (Adempas), iloprost (Ventavis) inhalation solution, treprostinil (Tyvaso, Tyvaso DPI), treprostinil (Orenitram), treprostinil injection (Remodulin), and selexipag (Uptravi)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **OR**
      1. Member is three years of age or older and request is for bosentan (generic, Tracleer); **AND**
   B. Medication is prescribed by, or in consultation with, cardiologist or pulmonologist; **AND**
   C. A diagnosis of one of the following:
      1. Pulmonary arterial hypertension (PAH) (WHO) Group 1 with WHO Functional Class II-IV symptoms); **AND**
         a. An acute vasoreactivity test has been performed; **AND**
            i. Results were negative; **OR**
            ii. Results were positive; **AND**
               1. Treatment with a calcium channel blocker (CCB) (e.g. amlodipine, diltiazem, felodipine, nifedipine, nicardipine, or verapamil) has been ineffective after three months of therapy, unless contraindicated, or not tolerated; **AND**
         b. The request is for <u>generic ambrisentan, generic bosentan, macitentan (Opsumit), or riociguat (Adempas)</u>; **OR**
            i. The request is for <u>brand</u> <u>ambrisentan (Letairis)</u>; **AND**
               1. Generic ambrisentan has been ineffective, contraindicated, or not tolerated; **OR**
            ii. The request is for <u>brand</u> <u>bosentan (Tracleer)</u>; **AND**
               1. Generic bosentan has been ineffective, contraindicated, or not tolerated; **OR**
         c. The request is for <u>iloprost (Ventavis) inhalation solution, treprostinil (Tyvaso) inhalation solution, treprostinil dry powder inhalation (Tyvaso DPI), treprostinil (Orenitram) or selexipag (Uptravi)</u>; **AND**

i. Treatment with TWO of the following groups has been ineffective, contraindicated, or not tolerated:
    1. Endothelin receptor antagonist [e.g., bosentan (Tracleer), ambrisentan (Letairis), or macitentan (Opsumit)]
    2. Phosphodiesterase type 5 (PDE5 inhibitor) [e.g., sildenafil, tadalafil]
    3. Adempas (riociguat)

d. The request is for treprostinil injection solution; **AND**
    i. The request is for the generic treprostinil injection; **OR**
        1. Request is for brand Remodulin and generic treprostinil injection solution has been ineffective, contraindicated, or not tolerated; **AND**
    ii. Member has WHO Class IV symptoms or is classified as high risk (poor prognosis) [*see appendix table 1*]; **OR**
        1. The member is classified as low risk (good prognosis); **AND**
            a. Treatment with TWO of the following groups has been ineffective, contraindicated, or not tolerated:
                i. Endothelin receptor antagonist [e.g., bosentan (Tracleer), ambrisentan (Letairis), or macitentan (Opsumit)]
                ii. Phosphodiesterase type 5 (PDE5 inhibitor) [e.g., sildenafil, tadalafil]
                iii. Adempas (riociguat); **OR**
    iii. Member is transitioning from epoprostenol to treprostinil (Remodulin)

2. Persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) (WHO Group 4); **AND**
    i. Member has inoperable CTEPH; **OR**
    ii. Member had a surgery for CTEPH performed; **AND**
    iii. The request is for riociguat (Adempas); **OR**

3. Pulmonary Hypertension (PH) Due to Interstitial Lung Disease (ILD) (WHO Group 3); AND
    i. Diagnosis confirmed with chest high-resolution computed tomography (HRCT) imaging**; AND**
    ii. Diagnosis confirmed with a right heart catheterization (RHC)**; AND**
    iii. Member does NOT have PH caused by obstructive lung disease (e.g., chronic obstructive pulmonary disease [COPD], bronchiectasis) or hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation); **AND**
    iv. The request is for treprostinil (Tyvaso) inhalation solution or treprostinil dry powder inhalation (Tyvaso DPI)

II. Ambrisentan (Letairis) is considered investigational when used for all other conditions including but not limited to:
   A. Chronic thromboembolic pulmonary hypertension (CTEPH)
   B. Digital ulcers in systemic sclerosis
   C. Lowering Portal Pressure in Patients with Liver Cirrhosis
   D. Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis
   E. Sarcoidosis

III. Bosentan (Tracleer) is considered investigational when used for all other conditions including but not limited to:
   A. Chronic obstructive pulmonary disease - Pulmonary hypertension
   B. Chronic thromboembolic pulmonary hypertension (CTEPH)
   C. Digital ulcers in systemic sclerosis
   D. Essential hypertension
   E. Raynaud phenomenon in systemic sclerosis
   F. Thromboembolic pulmonary hypertension, chronic

IV. Macitentan (Opsumit) is considered investigational when used for all other conditions including but not limited to:
   A. Chronic thromboembolic pulmonary hypertension (CTEPH)
   B. Digital ulcers in systemic sclerosis
   C. Glioblastoma

V. Riociguat (Adempas) is considered investigational when used for all other conditions including but not limited to:
   A. Systemic sclerosis-associated digital ulcers

VI. Treprostinil (Tyvaso; Tyvaso DPI) is considered investigational when used for all other conditions including but not limited to:
   A. Pulmonary hypertension (PH) WHO Groups II-V
      - Group II - Left heart disease, including congestive heart failure (CHF)
      - Group III – Chronic obstructive pulmonary disease (COPD), bronchiectasis; Hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation)
      - Group IV - Chronic thrombotic and/or embolic disease
      - Group V - Sarcoidosis
   B. Chronic thromboembolic pulmonary hypertension (CTEPH)

VII. Iloprost (Ventavis), treprostinil (Orenitram, Remodulin) and selexipag (Uptravi) are considered investigational when used for all other conditions, including but not limited to:
   A. Pulmonary hypertension (PH) WHO Groups II-V

- Group II - Left heart disease, including congestive heart failure (CHF)
- Group III - Lung diseases, including chronic obstructive pulmonary disease (COPD), bronchiectasis, and idiopathic pulmonary fibrosis (IPF); Other lung disease with mixed obstruction and restriction (e.g., pulmonary fibrosis with emphysema; Hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation)
- Group IV - Chronic thrombotic and/or embolic disease
- Group V – Sarcoidosis

B. Chronic thromboembolic pulmonary hypertension (CTEPH)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Member has exhibited improvement or stability of disease symptoms (e.g. improved exercise capacity and tolerance, reduced number of hospitalizations, improvement in WHO functional class).

Supporting Evidence

I. Patients with PH are classified into five clinical groups based on cause of PH.
   a. Group 1: pulmonary arterial hypertension (PAH) which has several causes (e.g., inheritable causes, drugs, connective tissue disease)
   b. Group 2: PH due to left-sided heart disease
   c. Group 3: PH due to chronic lung disorders and hypoxemia
   d. Group 4: PH due to pulmonary artery obstructions
   e. Group 5: PH due to unidentified mechanisms

II. The safety and efficacy of bosentan (Tracleer) in pediatric patients was evaluated in an open-label, uncontrolled study with 19 pediatric PAH patients aged 3 to 15 years. Patients had primary pulmonary hypertension (n = 10) or PAH related to congenital heart diseases (9 patients) and were WHO functional class II or class III at baseline. Patients were dosed with bosentan for 12 weeks. Half of the patients in each group were already being treated with intravenous epoprostenol and the dose of epoprostenol remained constant for the duration of the study. Hemodynamics were measured in 17 patients. The mean decrease in (pulmonary vascular resistance) PVR was 389 dyn·sec·cm^{-5}, which was similar to the effect seen in adults. Hemodynamic improvements from baseline were similar with or without co-administration of epoprostenol.

*Normal PVR value is <250 dyn·sec·cm$^{-5,}$ but PAH patients, depending on the severity of the disease state, have a significantly higher PVR value. A Systematic Review and Meta-Analysis of 12 studies was done and baseline PVR value of the PAH patients included in the study was 668.6±219.1 <250 dyn·sec·cm^{-5}.

III. Clinical studies of ambrisentan (Letairis), macitentan (Opsumit), riociguat (Adempas), iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram) and selexipag (Uptravi) did not include patients younger than 18 years to determine whether they respond differently from older patients. Safety and efficacy in pediatric patients has not been established.

IV. PH is a progressive and life-threatening disease. The medications as well as the disease state should be managed by a specialist.

PAH

V. The American College of Chest Physicians (CHEST) guideline for Therapy for PAH in adults suggests that patients with PAH, in the absence of contraindications, should undergo acute vasoreactivity testing using a short-acting agent at a medical center with experience in the performance and interpretation of vasoreactivity testing. Contraindications to acute vasoreactivity testing include a low systemic BP, low CO, or the presence of FC IV symptoms. Patients who demonstrate acute vasoreactivity – in the absence of right-sided heart failure or contraindications to CCB therapy – according to consensus definition, should be considered candidates for a trial of therapy with an oral CCB. CCBs are considered primary therapy.

VI. Lacking head-to-head comparisons of pharmacologic agents for the treatment of PAH, there is insufficient evidence to determine if one agent is superior to another.

VII. Ambrisentan (Letairis), bosentan (Tracleer), and macitentan (Opsumit) are indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in adults to improve exercise ability and decrease clinical worsening.

a. Studies with bosentan (Tracleer) establishing effectiveness included predominantly patients with WHO Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%). The primary study endpoint was 6-minute walk distance; however, symptoms and functional status was also assessed. In both trials, treatment with Tracleer resulted in a significant increase in exercise ability. The improvement in walk distance was apparent after 1 month of treatment and fully developed by about 2 months of treatment.

b. Ambrisentan (Letairis) and macitentan (Opsumit) effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients who were included in this study had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), or PAH caused by congenital heart disease with repaired shunts (8%). The primary study endpoint was a 6-minute walk distance. An increase in 6-minute walk distance was observed after 4 weeks of treatment with Letairis, with a dose-response observed after 12 weeks of treatment.

c. Macitentan (Opsumit) effect on progression of PAH was demonstrated in a multi-center, long-term, placebo-controlled study in 742 patients with symptomatic PAH WHO FC II-IV. The primary study endpoints were time to the first occurrence of death, a significant morbidity event (defined as atrial septostomy), lung transplantation, initiation of IV or subcutaneous (SC) prostanoids, or “other worsening of PAH” during double-blind treatment plus 7 days. Other worsening was defined as all of the following: a sustained

≥15% decrease from baseline in 6MWD, worsening of PAH symptoms (worsening of WHO FC), and need for additional treatment for PAH. All of these other worsening events were confirmed by an independent adjudication committee, blinded to treatment allocation. Treatment with OPSUMIT 10 mg resulted in a 45% reduction in the occurrence of the primary endpoint.

VIII. Iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram), treprostinil (Remodulin), and selexipag (Uptravi) are synthetic analogs of prostacyclin indicated for the treatment of PAH (WHO Group 1) to improve a composite endpoint consisting of exercise tolerance, symptoms (WHO Class), and lack of deterioration. Injectable treprostinil (Remodulin) also carries FDA approval for transition from epoprostenol.

IX. Studies in Iloprost (Ventavis) establishing effectiveness included predominately patients with WHO Functional Class III-IV symptoms, etiologies of idiopathic or heritable PAH (65%), or PAH associated with connective tissue diseases (23%). The primary efficacy endpoint was clinical response at 12 weeks with a composite endpoint defined by: improvement in exercise ability (6-minute walk test) by at least 10% versus baseline evaluated 30 minutes after dosing, improvement with at least one WHO FC versus baseline, and no death or deterioration of pulmonary hypertension. The percentage of patients who had a minimum increase of at least 10 percent in the distance walked within six minutes at week 12 was slightly, but not significantly, higher in the iloprost group than in the placebo group. The absolute change in the 6MWD was significantly larger in the iloprost group. More patients in the iloprost group than in the placebo group had an improvement in the severity of heart failure, as assessed by the WHO FC.

X. Studies in treprostinil (Tyvaso) to establish effectiveness included predominately patients with WHO Functional Class III symptoms, etiologies of idiopathic or heritable PAH (56%), or PAH associated with connective tissue diseases (33%). While there is long-term data on use of treprostinil (Tyvaso) by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil (Tyvaso) has been on a background of bosentan (Tracleer) (an endothelin receptor antagonist) or sildenafil (Revatio) (a phosphodiesterase type 5 inhibitor).

XI. Per the package insert, the study in treprostinil (Orenitram), that established effectiveness included predominately patients with WHO functional class II-III symptoms, etiologies of idiopathic or heritable PAH (75%), or PAH associated with connective tissue disease (19%). When used as the sole vasodilator, the effect of treprostinil (Orenitram) on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this.

XII. Treprostinil injection (Remodulin) is indicated for subcutaneous or intravenous use only as a continuous infusion. The package insert states treprostinil injection is preferably infused subcutaneously but can be administered by a central intravenous line if the subcutaneous route is not tolerated. Treprostinil can be self-administered subcutaneously by continuous infusion, via a subcutaneous catheter, using an infusion pump designed for subcutaneous drug delivery. 2019 CHEST guidelines recommend use of treprostinil injection (Remodulin) for patients with continued progression of their disease, and/or markers of poor clinical prognosis despite treatment with one or two classes of oral agents; or in patients with WHO functional class IV.

XIII. Effectiveness of selexipag (Uptravi) was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms. Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), and PAH associated with congenital heart disease with repaired shunts (10%).

XIV. ACCF/AHA guidelines indicate oral ERA or PDE-5 inhibitor therapy as first line treatment for lower risk PAH patients. There is insufficient safety and efficacy evidence to establish that any one oral therapy for PAH is clearly superior to another. Treatment guidelines do support combination therapy of PDE, ERA, and prostanoid agents.

XV. For patients with WHO functional class II or III 2019 CHEST guidelines recommend the combination of ambrisentan and tadalafil as first line therapy. This is based on data from the AMBITION trial. The trial involved 605 patients with WHO functional class II or III PAH. Patients were randomly assigned to receive once-daily ambrisentan plus tadalafil or to either drug alone. Doses were titrated from 5-10 mg/day for ambrisentan and from 20-40 mg/day for tadalafil. Treatment with the combination was associated with an approximately 50% reduction in risk for clinical failure compared with either drug alone (*P* = .0002), with improved exercise ability as well as decreased disease progression and hospitalization.

XVI. The 2019 Chest guidelines recommend treatment naive PAH patients with WHO functional class II and III use combination therapy with ambrisentan and tadalafil to improve 6MWD. For patients who are unwilling or unable to tolerate combination therapy, advise monotherapy with a currently approved ERA, PDE-5 inhibitor, or the soluble guanylate cyclase stimulator riociguat. Guidelines suggest that parenteral or inhaled prostanoids not be chosen as initial therapy for treatment naive PAH patients with WHO FC II symptoms or as second line agents for PAH patients with WHO FC II symptoms who have not met their treatment goals.

CTEPH

XVII. Riociguat (Adempas) is a soluble guanylate cyclase (sGC) stimulator indicated for the treatment of adults with persistent/recurrent CTEPH after surgical treatment, inoperable CTEPH or PAH to improve exercise capacity and WHO functional class. Medical therapy prior to surgery is not indicated because there is no evidence to show it improves hemodynamic or mortality outcomes after surgery.

PH due to ILD

XVIII. WHO Group 3 PH can be further broken down to specific causes. Those causes are:

- Obstructive lung disease (e.g., COPD or bronchiectasis)
- Restrictive lung disease (e.g., ILD, kyphoscoliosis)
    - Other lung disease with mixed obstruction and restriction (eg, pulmonary fibrosis with emphysema)
- Hypoxia without lung disease (e.g., high altitude, sleep apnea, obesity hypoventilation)
- Developmental lung disorders (e.g., bronchopulmonary dysplasia, congenital lobar emphysema)

XIX. FDA approval for treprostinil (Tyvaso) is specific to PH associated with ILD as that was the population evaluated in clinical trials.

XX. The safety and efficacy of treprostinil (Tyvaso) inhalation solution for the treatment of patients with PH due to ILD was studied in a Phase 2/3, multicenter, randomized, double-blinded, placebo-controlled trial.
    a. Patients were adults with Group 3 pulmonary hypertension diagnosed by right heart catheterization. The mean age was 66.5 years, 46.9% were female and majority had the diagnosis of idiopathic interstitial pneumonia (in 44.8%).
    b. Primary efficacy outcome measure of difference between the two groups in the change in peak 6-minute walk distance from baseline to week 16 was met with a difference of 31.12 m (95% confidence interval [CI], 16.85 to 45.39; P<0.001).
    c. Clinical worsening was evaluated as a secondary endpoint and occurred in 37 patients (22.7%) in the treprostinil group, as compared with 54 patients (33.1%) in the placebo group (hazard ratio, 0.61; 95% CI, 0.40 to 0.92; P=0.04 by the log-rank test)
    d. There was no significant between-group difference in patient-reported quality of life as assessed with the SGRQ or in the distance–saturation product at week 16
    e. The most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea. Serious adverse events occurred in 23.3% of the patients who received inhaled treprostinil and in 25.8% of those who received placebo.

XXI. Patients who have shown intolerance or significant lack of efficacy to a prostacyclin or prostacyclin analogue that resulted in discontinuation or inability to effectively titrate that therapy were excluded from the clinical trial. There is a lack of clinical trial data to show that Treprostinil (Tyvaso) would be effective or safe in this patient population.

Investigational Uses

I. Ambrisentan (generic, Letairis);
    A. Chronic thromboembolic pulmonary hypertension (CTEPH)
        a. AMBER I is a phase 3, randomized, double-blind, placebo controlled, parallel group, 16-week study evaluating the safety and efficacy of ambrisentan and placebo in subjects with inoperable CTEPH. AMBER II is an open-label, extension study of the long-term safety, tolerability, and efficacy.
        b. These studies were terminated early due to futility of enrollment. This was due to several factors, including an unexpectedly low screening rate (~20% of expected) and high screening failure rate (approaching 60%, mostly due to concerns regarding inoperability raised by the central adjudication committee).
    B. Digital ulcers (DU) in systemic sclerosis
        a. A pilot study was conducted to evaluate the efficacy of ambrisentan in the treatment and prevention of digital ulcers in patients with systemic sclerosis and they found that ambrisentan did not prevent the development of new DU over a 4-week time period after 24 weeks. A placebo-controlled study with more patients will be necessary to conclusively assess the effects of ambrisentan on DUs. There is no robust data to support the use of ambrisentan in DUs.

C. Lowering Portal Pressure in Patients with Liver Cirrhosis
    a. A phase II, single-arm, open-label study to characterise the effect on portal pressure, the effect on renal function and the pharmacokinetic profile of ambrisentan in patients with decompensated cirrhosis is being conducted but no results have been published yet.
D. Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis
    a. A Phase 3, randomized, double-blind, placebo-controlled, multi-center, parallel-group study to evaluate the efficacy and safety of ambrisentan in subjects with idiopathic pulmonary fibrosis and pulmonary hypertension called ARTEMIS-PH was terminated.
E. Sarcoidosis
    a. Ambrisentan was studied for Sarcoidosis Associated Pulmonary Hypertension in a single group assignment, open-label clinical trial and suggested a possible benefit of this drug in selected patients. However, the study was a prospective, open-label, proof of concept trial of ambrisentan that wasn't powered enough to show robust safety and efficacy data to support the use.
    b. There is limited or no published clinical trial data to support the use of ambrisentan in conditions other than Pulmonary Arterial Hypertension (PAH). The clinical trials that were conducted either had very few patients, data was not published, or the studies were terminated.

II. Bosentan (Tracleer)
A. Chronic obstructive pulmonary disease - Pulmonary hypertension
    a. In a 12-week randomized trial (N=30) in patients with severe, or very severe, COPD who did not have severe pulmonary hypertension at rest, there was no significant between-group difference in change from baseline in the mean 6-minute walking distance. Additionally, from baseline to week 12, the mean arterial partial pressure of oxygen significantly decreased in the bosentan group compared with placebo. Health-related quality of life scores (Short-Form-36 Health Survey) also significantly worsened in the bosentan group compared with placebo.
    b. In a small, open-label study (N=32), addition of bosentan to best supportive care (BSC) improved the 6-minute walking distance and WHO functional class compared with patients receiving BSC alone. Bosentan plus BSC did not significantly improve baseline pulmonary volumes (functional vital capacity, forced expired volume in 1 second), cardiac index, arterial blood gases (partial pressure of oxygen and carbon dioxide), or quality of life (St. George questionnaire).
    c. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline does not recommend use of bosentan for treating patients with severe COPD.
B. Chronic Thromboembolic Pulmonary Hypertension (CTEPH)
    a. Bosentan was studied in a prospective, phase III, randomized, placebo-controlled, double-blind, multicenter, parallel group study to assess the efficacy, safety and tolerability in 157 patients with inoperable CTEPH (NCT00313222). The primary outcome was change from baseline to week 16 in 6MWD and change from baseline to week 16 in pulmonary vascular resistance (PVR) at rest. A statistically significant

treatment effect (TE) on PVR was demonstrated: -24.1% of baseline (95% confidence interval [CI]: -31.5% to -16.0%; p < 0.0001). Mean TE on 6-min walk distance was +2.2 m (95% CI: -22.5 to 26.8 m; p = 0.5449) which is not statistically significant.

b. The BENEFIT open-label, extension study in patients with inoperable CTEPH. In total, 148 of the patients who received randomized treatment rolled over into the extension. The trial data has not been published.

c. There is limited clinical trial data to support the use of bosentan in CTEPH. The clinical trial showed very limited efficacy and safety data.

C. Digital ulcers in systemic sclerosis

A. In a double-blind, placebo-controlled study, 122 patients with limited or diffuse systemic sclerosis, according to American College of Rheumatology criteria, and documented digital ulcer within the previous 12 months were randomized 2:1 to treatment with oral bosentan (79 patients) or placebo (43 patients). Mean patient age was 51.8 years, and 63% of patients had digital ulcers at baseline. In patients receiving bosentan, the number of new digital ulcers was significantly reduced compared with placebo (*P*=0.0083), averaging 1.4 and 2.7 new ulcers per patient, respectively. Of patients with digital ulcers at baseline, an average of 1.8 new ulcers occurred per bosentan-treated patient and an average of 3.6 new ulcers occurred per placebo-treated patient, a reduction of 50% (*P*=0.0075). There was a slight improvement in Scleroderma Health Assessment Questionnaire (SHAQ) scores that did not reach statistical significance, except for hand function which was significantly improved in bosentan-treated patients. In patients with diffuse scleroderma with digital ulcers at baseline, 11% of bosentan-treated patients developed 4 or more new ulcers and 0% developed 7 or more new ulcers, compared with 50% and 20% of patients in the placebo group. There was no significant difference in time to complete or partial healing of ulcers between groups; however, there was a slight trend toward slower healing in patients treated with bosentan. Adverse effects of bosentan included diarrhea (7 [8.9%] patients) and elevated transaminase levels (9 [11.4%] patients). Five patients in the bosentan group withdrew because of abnormal liver function tests.

D. Essential hypertension

a. There is no evidence that differentiates safety and efficacy of bosentan from other traditional medications (diuretics, CCB, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), and alfa and beta blockers).

E. Raynaud phenomenon in systemic sclerosis

a. Data from controlled and uncontrolled trials evaluating bosentan (Tracleer) in the management of secondary Raynaud phenomenon demonstrate conflicting results in clinical and microvascular assessments. According to evidence-based international consensus-derived recommendations, bosentan has no confirmed efficacy in the treatment of active digital ulcers in systemic sclerosis patients but is effective in the prevention of digital ulcers, particularly multiple ulcers, and should be considered after other therapies have failed.

F. Thromboembolic pulmonary hypertension, chronic

a. A systematic review identified 2 randomized trials of 182 patients with chronic thromboembolic pulmonary hypertension that compared 16 weeks of treatment with bosentan (Tracleer) versus placebo. Bosentan (Tracleer) significantly improved the cardiopulmonary hemodynamic parameters of cardiac index and pulmonary vascular resistance. Bosentan (Tracleer) did not significantly affect the 6-minute walk distance, mean pulmonary arterial pressure, risk of functional class deterioration, or risk of clinical worsening. The risk of liver function abnormality was significantly increased with bosentan (Tracleer).

III. Macitentan (Opsumit);

A. Chronic thromboembolic pulmonary hypertension (CTEPH)

a. The safety, tolerability and efficacy of macitentan in subjects with inoperable chronic thromboembolic pulmonary hypertension were evaluated in MERIT-1 and MERIT-2:

i. MERIT-1 is a prospective, randomized, placebo-controlled, double-blind, multicenter, parallel-group, 24-week study to assess the efficacy, safety and tolerability in 80 patients. The primary efficacy endpoint is defined as the pulmonary vascular resistance (PVR) at rest at week 16 expressed as percent of baseline PVR at rest and the geometric mean PVR at rest decreased to 73·0% (95% CI 63·6–83·8) of the baseline value in the macitentan group, corresponding to a mean decrease from baseline of 206 dyn·s/cm^5, and decreased to 87·2% (95% CI 78·5–96·7) of the baseline value in the placebo group, corresponding to a mean decrease from baseline of 86 dyn·s/cm^5 (ratio of geometric means 0·84, 95% CI 0·70–0·99, p=0·041). The trial did not include patients from the United States of America, included a small patient population and was short term.

ii. MERIT-2 is an ongoing, long-term, multicenter, single-arm, open-label extension study of the MERIT-1 study, to assess safety, tolerability and efficacy. Results from this trial have not been reported at this time.

b. There is insufficient clinical trial data to support the use of macitentan in patients with CTEPH. Clinical trials are ongoing to further evaluate macitentan for CTEPH.

B. Digital ulcers in systemic sclerosis

a. A prospective, randomized, placebo-controlled, double-blind, multicenter, parallel group study to assess the efficacy, safety and tolerability of macitentan in patients with ischemic digital ulcers associated with systemic sclerosis was terminated.

b. Two international, randomized, double-blind, placebo-controlled trials (DUAL-1, DUAL-2) were conducted in patients with systemic sclerosis and active digital ulcers at baseline. The primary outcome for each trial was the cumulative number of new digital ulcers from baseline to week 16. The results of the studies do not support the use of macitentan for the treatment of digital ulcers in this patient population.

C. Glioblastoma

a. A single-center, open-label, phase 1 study of concurrent therapy with macitentan, radiotherapy, and temozolomide, followed by maintenance therapy with macitentan

and temozolomide in subjects with newly diagnosed glioblastoma was terminated due to low recruitment.

b. A Phase 1/1b, open-label study in patients with recurrent glioblastoma to assess the safety and tolerability of macitentan in combination with dose-dense temozolomide was terminated because the results did not clearly support continuing development in recurrent GBM.

c. There is limited or no published clinical trial data to support the use of macitentan in conditions other than Pulmonary Arterial Hypertension (PAH). The clinical trials that were conducted had very few patients, no robust data, terminated, or data was not published.

IV. Riociguat (Adempas);

A. Systemic sclerosis-associated digital ulcers

a. Seventeen participants (eight placebo, nine riociguat) were randomized at five centers. Baseline characteristics were comparable between the treatment groups, except for participants who were randomized to placebo were older and had longer disease duration. Treatment with riociguat did not reduce the number of DU net burden compared with placebo at 16 weeks. Open-label extension suggests that longer duration is needed to promote DU healing, which needs to be confirmed in a new trial.

b. The conducted trials are not powered enough and show low or no efficacy. There is limited to no published clinical trial data to support the use of riociguat (Adempas) in conditions other than persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) or Pulmonary Arterial Hypertension (PAH).

VIII. Treprostinil (Tyvaso; Tyvaso DPI);

A. Pulmonary hypertension (PH) WHO Groups II-V

- Group II - Left heart disease, including congestive heart failure (CHF)
- Group III – Non-ILD lung diseases, including chronic obstructive pulmonary disease (COPD), bronchiectasis; Other lung disease with mixed obstruction and restriction (e.g., pulmonary fibrosis with emphysema); Hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation)
- Group IV - Chronic thrombotic and/or embolic disease
- Group V – Sarcoidosis

There is limited or no published clinical trial data to support the use of treprostinil (Tyvaso) in conditions other than PAH and PH due to ILD. The clinical trials that were conducted had very few patients, no robust data, were terminated, or data was not published.

IX. Iloprost (Ventavis), treprostinil (Orenitram) and selexipag (Uptravi);

A. Pulmonary hypertension (PH) WHO Groups II-V

- Group II - Left heart disease, including congestive heart failure (CHF)
- Group III - Lung diseases, including chronic obstructive pulmonary disease (COPD), bronchiectasis, and idiopathic pulmonary fibrosis (IPF); Other lung disease with mixed obstruction and restriction (e.g., pulmonary fibrosis with emphysema; Hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation)
- Group IV - Chronic thrombotic and/or embolic disease

- Group V – Sarcoidosis

B. There is limited or no published clinical trial data to support the use of iloprost (Ventavis), treprostinil (Orenitram) and selexipag (Uptravi) in conditions other than Pulmonary Arterial Hypertension (PAH). The clinical trials that were conducted had very few patients, no robust data, were terminated, or data was not published.

IV. Iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram) and selexipag (Uptravi);

A. Chronic thromboembolic pulmonary hypertension (CTEPH) – WHO Group IV

a. There is insufficient data to support the use of selexipag (Uptravi) in patients with inoperable or persistent/recurrent after surgical and/or interventional treatment CTEPH. Clinical trial was terminated as the study did not demonstrate efficacy on the primary endpoint, PVR vs. placebo at wk 20 at a planned interim analysis.

b. There is limited or no published clinical trial data to support the use of iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram) and selexipag (Uptravi) in conditions other than Pulmonary Arterial Hypertension (PAH). The clinical trials that were conducted had very few patients, no robust data, were terminated, or data was not published.

Appendix

I. Table 1: PAH Determinants of Prognosis (ACCF/AHA Guidelines)

Determinants of Risk	Lower Risk (Good Prognosis)	Higher Risk (Poor Prognosis)
Clinical evidence of RV failure	No	Yes
Progression of symptoms	Gradual	Rapid
WHO class†	II, III	IV
6MW distance‡	Longer (greater than 400 m)	Shorter (less than 300 m)
CPET	Peak VO2 greater than 10.4 mL/kg/min	Peak VO2 less than 10.4 mL/kg/min
Echocardiography	Minimal RV dysfunction	Pericardial effusion, significant RV enlargement/dysfunction, right atrial enlargement
Hemodynamics	RAP less than 10 mm Hg, CI greater than 2.5 L/min/m2	RAP greater than 20 mm Hg, CI less than 2.0 L/min/m2
BNP§	Minimally elevated	Significantly elevated
*Most data available pertains to IPAH. Little data is available for other forms of PAH. One should not rely on any single factor to make risk predictions.		
†WHO class is the functional classification for PAH and is a modification of the New York Heart Association functional class.		
‡6MW distance is also influenced by age, gender, and height.		
§As there is currently limited data regarding the influence of BNP on prognosis, and many factors including renal function, weight, age, and gender may influence BNP, absolute numbers are not given for this variable.		
6MW indicates 6-minute walk; BNP, brain natriuretic peptide. CI, cardiac index; CPET, cardiopulmonary exercise testing; peak VO2, average peak oxygen uptake during exercise; RAP, right atrial pressure; RV, right ventricle; and WHO, World Health Organization.		

References

1. Ambrisentan (Letairis®) [Prescribing Information]. Gilead Sciences, Inc., Foster City, CA. 04/23/2019
2. Bosentan (Tracleer®) [Prescribing Information]. Actelion Pharmaceuticals US, Inc. South San Francisco, CA. June 2015
3. Macitentan (Opsumit®) [Prescribing Information]. Actelion Pharmaceuticals US, Inc. South San Francisco, CA. 04/23/2019
4. Riociguat (Adempas) [package insert].Wayne, NJ: Bayer HealthCare Pharmaceuticals Inc.; 2013.
5. Iloprost (Ventavis®) [Prescribing Information]. South San Francisco, CA; Actelion Pharmaceuticals US, Inc. 10/16/2017
6. Treprostinil (Tyvaso®) [Prescribing Information]. Research Triangle Park, NC: United Therapeutics Corp. 03/2021
7. Treprostinil (Orenitram®) [Prescribing Information]. Research Triangle Park, NC: United Therapeutics Corp. 01/24/2017
8. Selexipag (Uptravi®) [Prescribing Information]. South San Francisco, CA; Actelion Pharmaceuticals US, Inc. 09/04/2019
9. Barst RJ, Ivy D, Dingemanse J, Widlitz A, Schmitt K, Doran A, Bingaman D, Nguyen N, Gaitonde M, van Giersbergen PL. Pharmacokinetics, safety, and efficacy of bosentan in pediatric patients with pulmonary arterial hypertension. (n.d.). Clinical Pharmacology & Therapeutics, 73(4), 372–382. doi: https://doi.org/10.1016/S0009-9236(03)00005-5 https://www.ncbi.nlm.nih.gov/pubmed/12709727
10. Berger RM, Haworth SG, Bonnet D, Dulac Y, Fraisse A, Galiè N, Ivy DD, Jaïs X, Miera O, Rosenzweig EB, Efficace M, Kusic-Pajic A, Beghetti M. FUTURE-2: Results from an open-label, long-term safety and tolerability extension study using the pediatric Formulation of bosentan in pulmonary arterial hypertension. Int J Cardiol. 2016 Jan 1;202:52-8. doi: 10.1016/j.ijcard.2015.08.080 https://www.ncbi.nlm.nih.gov/pubmed/26386921
11. Galie N, et al. Updated treatment algorithm of pulmonary arterial hypertension. J Am Coll Cardiol. 2013 Dec 24;62(25 Suppl): D60-72.
12. Taichman DB, et al. Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST guideline and expert panel report. CHEST 2019 Aug; 146(2). 449-75.
13. Galie N, et al. Updated treatment algorithm of pulmonary arterial hypertension. J Am Coll Cardiol. 2013 Dec 24;62(25 Suppl): D60-72.
14. McLaughlin VV, Archer SL, 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. Circulation. 2009;119(16):2250-2294.
15. Galie, Nazzareno MD; Olschewski, Horst MD; Oudiz, Ronald J. MD; Torres, Fernando MD. Ambrisentan for the Treatment of Pulmonary Arterial Hypertension: Results of the Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy (ARIES) Study 1 and 2. Circulation. 117(23), 10 June 2008. DOI: 10.1161/CIRCULATIONAHA.107.742510 PMID: 18506008
16. K Ahmadi-Simab;P Lamprecht;B Hellmisch. Treatment of pulmonary arterial hypertension (PAH) with oral endothelin-receptor antagonist bosentan in systemic sclerosis: BREATHE-1 trial and clinical experience. 63(6). 495-497. DOI: 10.1007/s00393-004-0594-3 PMID: 15605216
17. N. Channick MD; Marion Delcroix MD; Hossein-Ardeschir Ghofrani MD; Elke Hunsche PhD. Effect of Macitentan on Hospitalizations: Results from the SERAPHIN Trial. January 2015. 3(1). 1-8. https://doi.org/10.1016/j.jchf.2014.07.013
18. Horst Olschewski, M.D., Gerald Simonneau, M.D., Nazzareno Galiè, M.D., Timothy Higenbottam, M.D. et. Inhaled Iloprost for Severe Pulmonary Hypertension. New England Journal of Medicine 2002; 347:322-329 DOI: 10.1056/NEJMoa020204 PMID: 25457902
19. Wilkins, MR, Paul, GA, Strange, JW, et al. Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension (SERAPH) study. Am J Respir Crit Care Med. 2005 Jun 1;171(11):1292-7. PMID: 15750042
20. Korn JH, Mayes M, Matucci Cerinic M, et al. Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. Arthritis Rheum. 2004;50(12):3985-3993.[PubMed 15593188]
21. Chen X, Zhai Z, Huang K, et al: Bosentan therapy for pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: a systemic review and meta-analysis. Clin Respir J 2018; 12(6):2065-2074.

PubMed Abstract: http://www.ncbi.nlm.nih.gov/...
PubMed Article: http://www.ncbi.nlm.nih.gov/...
22. Gilead Sciences. ARTEMIS-PH - Study of Ambrisentan in Subjects With Pulmonary Hypertension Associated With Idiopathic Pulmonary Fibrosis (ARTEMIS-PH). ClinicalTrials.gov Identifier: NCT00879229
23. Noorik Biopharmaceuticals AG. A Study Evaluating the Utility of Ambrisentan in Lowering Portal Pressure in Patients with Liver Cirrhosis. ClinicalTrials.gov Identifier: NCT03827200
24. Medical University of South Carolina, Gilead Sciences. Ambrisentan (Letairis) for Sarcoidosis Associated Pulmonary Hypertension. ClinicalTrials.gov Identifier: NCT00851929
25. Judson MA, Highland KB, Kwon S, Donohue JF, Aris R, Craft N, Burt S, Ford HJ. Ambrisentan for sarcoidosis associated pulmonary hypertension. Sarcoidosis Vascular Diffuse Lung Dis. 2011 Oct; 28(2):139-45. PMID: 22117505
26. Chung L, Ball K, Yaqub A, Lingala B, Fiorentino D. Effect of the endothelin type A-selective endothelin receptor antagonist ambrisentan on digital ulcers in patients with systemic sclerosis: results of a prospective pilot study. J Am Acad Dermatol. 2015. 71(2): 400–401. doi: 10.1016/j.jaad.2014.04.028 PMID: 25037794
27. Actelion. Macitentan for the Treatment of Digital Ulcers in Systemic Sclerosis Patients (DUAL-2). ClinicalTrials.gov Identifier: NCT01474122
28. Dinesh Khanna, MD; Christopher P. Denton, MD; Peter A. Merkel, MD; et al. Effect of Macitentan on the Development of New Ischemic Digital Ulcers in Patients With Systemic Sclerosis DUAL-1 and DUAL-2 Randomized Clinical Trials. JAMA. 2016; 315(18):1975-1988. doi:10.1001/jama.2016.5258
29. Actelion. Clinical Study on Macitentan, RT and TMZ Concurrent Therapy Followed by Maintenance Macitentan and TMZ in Newly Diagnosed Glioblastoma. ClinicalTrials.gov Identifier: NCT02254954
30. Actelion. Clinical Study on the Safety and Tolerability of Macitentan in Combination with Dose-dense Temozolomide in Patients with Recurrent Glioblastoma. ClinicalTrials.gov Identifier: NCT01499251
31. Nagaraja V, Spino C, Bush E, Tsou PS, Domsic RT, Lafyatis R, Frech T, Gordon JK, Steen VD, Khanna D. A multicenter randomized, double-blind, placebo-controlled pilot study to assess the efficacy and safety of riociguat in systemic sclerosis-associated digital ulcers. Arthritis Res Ther. 2019 Sep 3; 21(1):202. doi: 10.1186/s13075-019-1979-7.
32. Up-to-Date. Treatment of Pulmonary Hypertension in Adults. Accessed via: https://www.uptodate.com/contents/treatment-of-pulmonary-arterial-hypertension-group-1-in-adults-pulmonary-hypertension-specific-therapy?search=pulmonary%20hypertension&source=search_result&selectedTitle=2%7E150&usage_type=default&display_rank=2on January 13, 2016.
33. Valerio G, Bracciale P, & Grazia D'Agostino A: Effect of bosentan upon pulmonary hypertension in chronic obstructive pulmonary disease. Ther Adv Respir Dis 2009; 3(1):15-21.
34. Aaron Waxman, M.D., Ph.D., et al. Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease. N Engl J Med 2021; 384:325-334 DOI: 10.1056/NEJMoa2008470
35. Ganesh Raghu, et al. Diagnosis of Idiopathic Pulmonary Fibrosis An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2018. 198, 5. e44–e68, DOI: 10.1164/rccm.201807-1255ST
36. 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.
37. Remodulin[treprostinil) [package insert] United Therapeutics Corp; Research Triangle Park, NC. Revised July 2018
38. Tyvaso DPI [treprostinil) [package insert] United Therapeutics Corp; Research Triangle Park, NC. Revised May 2022

Policy Implementation/Update:

Action and Summary of Changes	Date
Added Tyvaso DPI product. In the setting of PAH: Updated oral and inhaled prostoninoids (e.g., treopostinil) to require previous trial of two within a PDE-5, ERA, or riociguat. Removed requirement of a PDE-5 prior to approval of an ERA. Updated initial approval duration to be 6 months for all products.	04/2023
• Added new indication of PH due to ILD for treprostinil (Tyvaso) • Added treprostinil injection (Remodulin) into policy • Removed requirement of PDE-5 monotherapy for 3 months in those requesting generic ambrisentan in combination with a PDE-5 • Added requirement of prior endothelin receptor antagonist if requesting Ventavis or Tyvaso in PAH	06/2021
• Updated renewal section with standard renewal language	03/2020

• Added chronic thromboembolic pulmonary hypertension (CTEPH) as an investigational indication to bosentan (generic, Tracleer), ambrisentan (generic, Letairis), macitentan (Opsumit) and selexipag (Uptravi)	
• Updated the criteria into policy format • Added acute vasoreactivity test criteria to apply to all agents • Added age limit to reflect clinical trial data • Combined criteria for bosentan (generic, Tracleer), ambrisentan (generic, Letairis)& macitentan (Opsumit) with riociguat (Adempas) criteria and Iloprost (Ventavis), treprostinil (Tyvaso and Orenitram), selexipag (Uptravi) • Quantity limit change iloprost (Ventavis) and bosentan (Letairis) to reflect the dosing in the package insert • Treprostinil (Orenitram) 5mg doseage form added • Added criteria because generic bosentan and generic ambrisentan became available we are driving patients to a more cost effective option; o Prior to getting bosentan (Tracleer), member has tried generic bosentan and treatment has been ineffective, contraindicated, or not tolerated o Prior to getting ambrisentan (Letairis), member has tried generic ambrisentan and treatment has been ineffective, contraindicated, or not tolerated • Added generic bosentan and generic ambrisentan to the policy	12/2019
• Added Uptravi for P&T 5/4/16 • Reviewed policy	3/29/2016
• Updated formatting. • Added Tyvaso and Orenitram, removed question regarding initial 6 minute walking distance and required trial and failure of generic sildenafil only for oral prostanoid.	03/17/2016
• Criteria update: Validated place in therapy and recommendations. • Removed questions regarding contraindications, warnings/precautions. • Updated header, footer and formatting [riociguat (Adempas)] • Reviewed	03/14/2016
Policy created and effective [iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram) and selexipag (Uptravi)]	Prior to 3/17/2016 (no date available)
Policy created [ambrisentan (Letairis), bosentan (Tracleer) and macitentan (Opsumit)]	03/2016
Previously reviewed [ambrisentan (Letairis), bosentan (Tracleer) and macitentan (Opsumit)]	03/2014, 03/2016
Criteria for ambrisentan (Letairis), bosentan (Tracleer) and macitentan (Opsumit) created	01/2013

Policy Type: PA/SP Pharmacy Coverage Policy: UMP234

Description

Pyrimethamine (Daraprim) is an orally administered antiparasitic agent that reversibly inhibits the protozoal enzyme dihydrofolate reductase, selectively blocking conversion of dihydrofolic acid to its functional form, tetrahydrofolic acid.

Length of Authorization

I. Initial: Six months
II. Renewal:
  i. **Congenital toxoplasmosis:** Six months, maximum one-time renewal
  ii. **All other indications:** 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit	
			Pediatric	Adult
Pyrimethamine (Daraprim)	25 mg tablets	Toxoplasmosis prophylaxis	30 tablets / 30 days	30 tablets / 30 days
		Toxoplasmosis treatment	30 tablets / 30 days	**First month:** 98 tablets / 30 days **Maintenance:** 90 tablets / 30 days
		Congenital toxoplasmosis	**First six months:** 30 tablets / 30 days **Last six months:** 10 tablets / 30 days	N/A
		Pneumocystis jiroveci pneumonia prophylaxis	N/A	30 tablets / 30 days
		Cystoisosporiasis (isosporiasis) treatment	30 tablets / 30 days	90 tablets / 30 days

Initial Evaluation

I. **Generic or compound pyrimethamine (Daraprim)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, an infectious disease specialist; **AND**
   B. Treatment with pyrimethamine compound formulation (e.g., solution, suspension, capsule) has been ineffective, contraindicated, or not tolerated; **AND**
   C. A diagnosis of one of the following:
      1. **Toxoplasmosis prophylaxis; AND**
         i. Documentation that the member is in an immunocompromised state (e.g., AIDS/HIV, transplant, cancer, or taking immunosuppressive drugs [e.g., corticosteroids, non-biologic, non-specialty DMARD (e.g., methotrexate, cyclosporine, acitretin, azathioprine, etc.), mycophenolate, biologics (e.g., adalimumab, etanercept), etc.]); **AND**
         ii. Seropositive for anti-toxoplasma immunoglobulin G (IgG); **AND**
         iii. Documentation that treatment with trimethoprim- sulfamethoxazole (TMP-SMX) has been ineffective, contraindicated, or not tolerated; **AND**
         iv. Treatment with pyrimethamine will be used in combination with leucovorin and an antimicrobial agent (e.g., sulfonamide [sulfadiazine, sulfamethoxazole/trimethoprim], dapsone, clindamycin, or atovaquone); **OR**
      2. **Toxoplasmosis treatment**
         i. Seropositive for anti-toxoplasma immunoglobulin G (IgG); **AND**
            a. Presence of active radiographic changes (one or more contrast-enhancing lesions, edema); **OR**
            b. Presence of clinical symptoms (e.g., fever, lymphadenopathy, chorioretinitis, headache, or motor weakness); **AND**
         ii. Treatment with pyrimethamine will be used in combination with leucovorin and an antimicrobial agent (e.g., sulfonamide [sulfadiazine, sulfamethoxazole/trimethoprim], dapsone, clindamycin, or atovaquone); **OR**
      3. **Congenital toxoplasmosis**; **AND**
         i. Treatment with pyrimethamine will be used in combination with leucovorin and an antimicrobial agent (e.g., sulfonamide [sulfadiazine, sulfamethoxazole/trimethoprim], dapsone, clindamycin, or atovaquone); **OR**
      4. ***Pneumocystis jiroveci* pneumonia (PCP) prophylaxis; AND**
         i. Documentation that the member is in an immunocompromised state (e.g., AIDS/HIV, transplant, cancer, or taking immunosuppressive drugs [e.g., corticosteroids, non-biologic, non-specialty DMARD (e.g., methotrexate, cyclosporine, acitretin, azathioprine, etc.), mycophenolate, biologics (e.g., adalimumab, etanercept), etc.]); **AND;**
         ii. Treatment with pyrimethamine will be used in combination with leucovorin and an antimicrobial agent (e.g., sulfonamide [sulfadiazine, sulfamethoxazole/trimethoprim], dapsone, clindamycin, or atovaquone); **AND**
         iii. Treatment with trimethoprim- sulfamethoxazole (TMP-SMX) has been ineffective or contraindicated; **OR**

iv. Treatment with trimethoprim- sulfamethoxazole (TMP-SMX) has been not tolerated; **AND**
    a. Member has been re-challenged with trimethoprim-sulfamethoxazole (TMP-SMX) using a desensitization protocol, or and is still unable to tolerate**; OR**

5. **Cystoisosporiasis treatment; AND**
    i. Treatment with pyrimethamine will be used in combination with leucovorin; **AND**
    ii. Treatment with one of the following has been ineffective, contraindicated, or not tolerated:
        a. Oral trimethoprim- sulfamethoxazole (TMP-SMX)**; OR**
        b. IV trimethoprim- sulfamethoxazole (TMP-SMX)**; OR**
        c. Ciprofloxacin

II. **Brand pyrimethamine (Daraprim)** may be considered medically necessary when the following criteria below are met:
    A. Criteria I(A)-I(C) above are met; **AND**
    B. In the absence of a drug shortage, coverage of the multi-source brand drug is to be considered medically necessary when the prescriber is requesting the multi-source brand drug due to a documented adverse reaction to the generic equivalent; **AND**
    C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
    D. The prescriber must document one or more of the following, indicating that the reaction:
        1. Was life-threatening; **OR**
        2. Required hospitalization; **OR**
        3. Required intervention to prevent impairment or damage; **OR**
    E. The prescriber is requesting the brand name drug due to a documented allergy to the generic equivalent [i.e., skin rashes (particularly hives), itching, respiratory compilations and angioedema] that required medical intervention to prevent impairment or damage; **OR**
    F. The prescriber is requesting the brand name drug due to a documented intolerance to the generic equivalent which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
        1. More than one generic equivalent has been tried, or there is only one generic equivalent for the prescribed brand drug.

III. Pyrimethamine (Daraprim) is considered not medically necessary when criteria above are not met and/or when used for:
    A. Prevention or treatment of malaria.

IV. Pyrimethamine (Daraprim) is considered investigational when used for all other conditions.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (e.g., CD4 count recovery, contrast-enhancing lesions, improvement in symptoms such as fever, lymphadenopathy, chorioretinitis, or headache); **AND**
IV. Request is for compound pyrimethamine; **OR**
V. If request is for generic pyrimethamine:
    a. Provider attests that the member remains ineligible to transition to compounded pyrimethamine products (e.g., solution, suspension, or capsule); **OR**
VI. If the request is for Brand Daraprim:
    a. Provider attests that the member remains ineligible to transition to compounded pyrimethamine products (e.g., solution, suspension, or capsule) or generic pyrimethamine tablets.

Supporting Evidence

I. Pyrimethamine (Daraprim) is not considered a narrow therapeutic index drug, therefore there are no foreseeable pharmacokinetic or clinical implications in transitioning a patient from an oral generic formulation to a compounded formulation.
II. There is no universal standard scale for quantifying an immunocompromised state. The National institute of Health National Cancer Institute defines immunocompromised (also called immunosuppressed) as having a weakened immune system and reduced ability to fight infections and other diseases. This may be caused by certain conditions, such as AIDS, cancer, diabetes, malnutrition, and certain genetic disorders. It may also be caused by certain treatments, such as biologics, corticosteroids, DMARDS, oncolytics, radiation therapy, and stem cell or organ transplant.
III. Opportunistic infections (OIs) are illnesses that occur more frequently and are more severe in people with compromised immune systems, including HIV, hematopoietic cell transplant, solid organ transplant, cancer-related immunosuppression and hematological malignancies, or taking immunosuppressive therapies. Due to the complexity of opportunistic infections, pyrimethamine needs to be prescribed by, or in consultation with, an infectious disease specialist.
IV. Initial serological screening should be performed to determine whether the member has ever been infected or is acutely or chronically infected with toxoplasmosis. *Toxoplasma*-specific IgG and IgM tests can be performed at any commercial, non-reference, or hospital-based laboratory. A positive serologic anti-toxoplasma IgG antibody test establishes that the member has been infected and is at risk of reactivation during periods of significant immunosuppression.
V. Pyrimethamine must be taken in combination with leucovorin and an antimicrobial agent due to enhanced safety and efficacy. Administration with leucovorin is recommended to reduce incidence of hematologic adverse events (myelosuppression) while taking pyrimethamine. Pyrimethamine and

an antimicrobial agent act synergistically by inhibiting proliferation and survival through inhibiting the folate metabolic pathway.

VI. **Toxoplasmosis prophylaxis**

a. TMP-SMX should be considered first line therapy for toxoplasmosis prophylaxis. TMP-SMX also provides protection against other pathogens, including PCP, Nocardia, enteric pathogens, Plasmodium species, urinary pathogens, and some respiratory pathogens. The broader spectrum of activity of TMP-SMX is among the reasons this drug is preferred.

b. In adults and adolescents with HIV, toxoplasmosis prophylaxis should be discontinued in patients receiving ART whose CD4 counts increase to >200 cells/mm3 for more than 3 months. Toxoplasmosis prophylaxis should be discontinued because it adds little value in preventing toxoplasmosis and increases pill burden, potential for drug toxicity and interaction, and likelihood of development of drug-resistant pathogens.

c. There is no consensus concerning initiation and duration of toxoplasmosis prophylaxis in immunocompromised members. Regarding the incidence rate of toxoplasmosis following hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT), prophylaxis should be maintained for at least 6 months post-transplant. It should be prolonged in cases of graft-versus-host disease, prolonged neutropenia, and prolonged administration of corticosteroids.

d. In immunocompetent individuals, acute toxoplasmosis infection is usually self-limited and rarely symptomatic, although cases of severe infection due to rare Toxoplasma genotypes have been reported. Treatment for toxoplasmosis is not required for immunocompetent members who are asymptomatic or have mild, uncomplicated acute toxoplasmosis.

VII. **Toxoplasmosis treatment**

a. Toxoplasmosis therapy requires serologic anti-toxoplasma IgG detection, radiographic changes (CT or MRI with multiple contrast-enhancing lesions in the grey matter of the cortex or basal ganglia, often with associated edema), and/or presence of clinical symptoms. Common clinical manifestations include lymphadenopathy, chorioretinitis (a type of posterior uveitis), headache, confusion, and motor weakness. The radiologic goals for treatment include resolution of the lesion(s) in terms of size, contrast enhancement, and associated edema, although residual contrast-enhancing lesions may persist for prolonged periods

b. In members with HIV, acute therapy for toxoplasmosis must be continued for at least 6 weeks. Longer courses may be necessary if clinical or radiologic disease is extensive, or response is incomplete at 6 weeks. After completion of the acute therapy, guidelines recommend members who have completed a 6-week treatment course for acute toxoplasmosis therapy should be given chronic maintenance therapy to suppress infection until immune reconstitution occurs as a consequence of antiretroviral therapy (ART). Members receiving chronic maintenance therapy for toxoplasmosis are at low risk for recurrence if they have successfully completed initial therapy, remain asymptomatic regarding signs and symptoms of toxoplasmosis, and have an increase in their CD4 counts to >200 cells/mm3 after ART that is sustained for more than 6 months.

VIII. **Congenital toxoplasmosis**

a. Pregnant women with suspected or confirmed primary toxoplasmosis and newborns with possible or documented congenital toxoplasmosis should be managed in consultation with an appropriate infectious disease specialist. Empiric therapy should be strongly considered for newborns of HIV-infected mothers who had symptomatic or asymptomatic primary

Toxoplasma infection during pregnancy, regardless of whether treatment was administered during pregnancy. The recommended duration of treatment for congenital toxoplasmosis in infants is 12 months (continuously throughout the first year of life).

IX. ***Pneumocystis jiroveci* pneumonia (PCP) prophylaxis**

a. The preferred PCP prophylaxis regimen for HIV and immunocompromised non-HIV infected patients is TMP-SMX, because of its superior efficacy compared with aerosolized pentamidine, oral dapsone, or oral atovaquone. TMP-SMX chemoprophylaxis should be continued, when clinically feasible, in patients who have non-life-threatening adverse reactions. In those who discontinue TMP-SMX because of a mild adverse reaction, re-institution of the drug should be considered after the reaction has resolved. Oral desensitization regimens have been used successfully for HIV-infected patients with fever and rash, and similar protocols have been used in HCT recipients with a success rate of approximately 80%. Therapy should be permanently discontinued (with no rechallenge) in patients with life-threatening adverse reactions including possible or definite Stevens-Johnson syndrome or toxic epidermal necrolysis.

b. PCP prophylaxis should be discontinued in adult and adolescent members who have responded to ART with an increase in CD4 counts from 200 cells/mm3 for >3 months. Discontinuation of primary PCP prophylaxis in patients with CD4 count increase to >200 cells/mm3 as a result of ART is recommended because its preventive benefits against PCP, toxoplasmosis, and bacterial infections are limited; stopping the drugs reduces pill burden, cost, and the potential for drug toxicity, drug interactions, and selection of drug-resistant pathogens.

c. PCP prophylaxis and treatment with pyrimethamine is not indicated for pediatric members. TMP–SMX is a first line prophylaxis agent due to its high efficacy, relative safety, low cost, and broad antimicrobial spectrum. Dapsone or atovaquone are second line effective and safe prophylaxis regimens available for pediatric patients unable to take TMP-SMX.

X. **Cystoisosporiasis treatment**

a. Cystoisosporiasis (also known as isosporiasis) should not be confused with Cryptosporidiosis. Cystoisosporiasis has also been reported immunocompromised as well as in immunocompetent individuals. In adults and adolescents with HIV, chemoprophylaxis with oral trimethoprim-sulfamethoxazole (TMP-SMX) has been associated with a lower incidence or prevalence of isosporiasis. Intravenous administration of TMP-SMX should be considered for patients with potential or documented malabsorption. Ciprofloxacin is considered a second-line alternative.

b. In a randomized, placebo-controlled trial, daily TMP-SMX (160/800 mg) was protective against isosporiasis in persons with early-stage HIV infection (World Health Organization clinical stage 2 or 3 at enrollment). In an observational study, incidence of isosporiasis decreased after widespread introduction of antiretroviral therapy (ART), except in patients with CD4 counts <50 cells/mm^3. After adjustment for the CD4 T lymphocyte (CD4) cell count, the risk of isosporiasis was substantially lower in those receiving prophylaxis with TMP-SMX, sulfadiazine, or pyrimethamine.

XI. In the United States, the Office of Generic Drugs at the Food and Drug Administration (FDA) follows a rigorous review process to make sure that, compared to the brand name (or innovator) medications, the proposed generic medications:

a. Contain the same active/key ingredient
b. Have the same strength
c. Use the same dosage form (for instance, a table, capsule, or liquid) and
d. Use the same route of administration (for instance, oral, topical, or injectable)

XII. The FDA's review process also ensures that generic medications perform the same way in the human body and have the same intended use as the name brand medication. Healthcare professionals and consumers can be assured that FDA-approved generic drug products have met the same rigid manufacturing standards as the innovator drug. In addition, FDA inspects facilities to make certain the generic manufacturing, packaging, and testing sites pass the same quality standards as those of brand-name drugs.
    a. Thus, when an adverse reaction or allergy occurs to any medication (brand or generic), it is important to report to MedWatch.
    b. In order to keep effective medical products available on the market, the FDA relies on the voluntary reporting of these events. This information is used to maintain safety surveillance and to monitor if modifications in use or design of the product are warranted to increase patient safety.

XIII. It can be difficult to distinguish an allergy from a distinct adverse event related to the generic, therefore any event thought to be related to the medication should be reported to MedWatch.
    a. As defined by the American Academy of Allergy, Asthma, and Immunology, an allergic reaction occurs when the immune system overreacts to a substance, triggering an allergic reaction. Sensitivities to drugs may produce similar symptoms, but do not involve the immune system. Only 5-20% of adverse reactions to drugs are considered true allergic reactions. The chances of developing an allergy are higher when you take the medication frequently or when it is rubbed on the skin or given by injection, rather than taken by mouth. The most frequent types of allergic symptoms to medications include skin rashes (particularly hives), itching, respiratory complications and angioedema. The most severe form of immediate allergic reactions is anaphylaxis, and symptoms include hives, facial or throat swelling, wheezing, light-headedness, vomiting and shock.

Investigational or Not Medically Necessary Uses

I. The use of pyrimethamine for prophylaxis or treatment of malaria in adults is no longer recommended in the CDC Guidelines for the Treatment of Malaria in the United States.

Appendix

Please note, specific doses vary among non-HIV conditions. Dosing regimens listed below are not all inclusive. Please cross-reference compendia for member-specific dose.

I. Table 1: Recommendations for Preventing and Treating Toxoplasmosis in Adults and Adolescents with HIV[2]

Indication	Preferred regimen	Alternative regimens	Treatment duration
Toxoplasmosis Prophylaxis	TMP-SMX 1 DS PO daily	• TMP-SMX 1 DS PO three times weekly, or • TMP-SMX SS PO daily, or • Dapsone 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly, or • (Dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly, or • Atovaquone 1500 mg PO daily, or • (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily	• CD4 count >200 cells/ mm^3 for >3 months in response to ART; or • Can consider if CD4 count is 100-200 cells/ mm^3 and HIV RNA levels remain below limits of detection for at least 3-6 months **Indication for Restarting Primary Prophylaxis:** • CD4 count < 100 – 200 cells/ mm^3
Treating acute Toxoplasmosis*	**Induction: Pyrimethamine 200 mg PO once**, followed by dose based on body weight: Body weight ≤60 kg: • pyrimethamine 50 mg PO daily + sulfadiazine 1000 mg PO q6h + leucovorin 10–25 mg PO daily (can increase to 50 mg daily or BID) Body weight >60 kg: • pyrimethamine 75 mg PO daily + sulfadiazine 1500 mg PO q6h + leucovorin 10–25 mg PO daily (can increase to 50 mg daily or BID)	Preferred alternative for patients intolerant of sulfadiazine or who do not respond to pyrimethamine-sulfadiazine: • Pyrimethamine (leucovorin)‡ plus clindamycin 600 mg IV or PO q6h + must add additional agent for PCP prophylaxis, or • TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) (IV or PO) BID, or • Atovaquone 1500 mg PO BID + pyrimethamine (leucovorin)‡, or • Atovaquone 1500 mg PO BID + sulfadiazine, or • Atovaquone 1500 mg PO BID	• At least 6 weeks; longer duration if clinical or radiologic disease is extensive or response is incomplete at 6 weeks • After completion of the acute therapy, all patients should be continued on chronic maintenance therapy
Toxoplasmosis Chronic Maintenance Therapy	Pyrimethamine 25–50 mg PO daily + sulfadiazine 2000–4000 mg PO daily (in 2 to 4 divided doses) + leucovorin 10–25 mg PO daily	• Clindamycin 600 mg PO q8h + (pyrimethamine 25–50 mg + leucovorin 10–25 mg) PO daily; or • TMP-SMX DS 1 tablet BID, or • TMP-SMX DS 1 tablet daily, or • Atovaquone 750–1500 mg PO BID + (pyrimethamine 25 mg + leucovorin 10 mg) PO daily, or • Atovaquone 750–1500 mg PO BID + sulfadiazine 2000–4000 mg PO daily (in 2 to 4 divided doses), or • Atovaquone 750–1500 mg PO BID	• Successfully completed initial therapy, remain asymptomatic of signs and symptoms of toxoplasmosis, and CD4 count >200 cells/mm^3 for >6 months in response to ART **Criteria for Restarting Secondary Prophylaxis/Chronic Maintenance** • CD4 count <200 cells/ mm^3

* Acute toxoplasma treatment: if pyrimethamine is unavailable or there is a delay in obtaining it, TMP-SMX should be used in place of pyrimethamine-sulfadiazine. For patients with a history of sulfa allergy, sulfa desensitization should be attempted using one of several published strategies. Atovaquone should be administered until therapeutic doses of TMP-SMX are achieved.

‡ Pyrimethamine and leucovorin doses: Same as doses listed in Preferred Regimen for treating acute toxoplasmosis

Acronyms: ART = antiretroviral therapy; BID = twice daily; CD4 = CD4 T lymphocyte cell; DS = double strength; IV = intravenous; PCP = *Pneumocystis* Pneumonia; PO = orally; q(n)h = every "n" hour; SS = single strength; TMP-SMX = trimethoprim-sulfamethoxazole

II. Table 2. Dosing Recommendations for the Prevention and Treatment of Toxoplasmosis in HIV-Exposed and HIV-Infected Children[3]

Indication	Preferred regimen	Alternative regimens	Treatment Duration / Comments
Primary Prophylaxis	TMP-SMX 150/750 mg/m^2 body surface area once daily by mouth	**For Children Aged ≥1 Month:** • Dapsone 2 mg/kg body weight or 15 mg/ m^2 body surface area (maximum 25 mg) by mouth once daily, plus • Pyrimethamine 1 mg/kg body weight (maximum 25 mg) by mouth once daily, plus • Leucovorin 5 mg by mouth every 3 days **For Children Aged 1–3 Months and >24 Months:** • Atovaquone 30 mg/kg body weight by mouth once daily **Children Aged 4–24 Months:** • Atovaquone 45 mg/kg body weight by mouth once daily, with or without pyrimethamine 1 mg/kg body weight or 15 mg/m^2 body surface area (maximum 25 mg) by mouth once daily, plus • Leucovorin 5 mg by mouth every 3 days **Acceptable Alternative Dosage Schedules for TMP-SMX:** • TMP-SMX 150/750 mg/ m^2 body surface area per dose once daily by mouth 3 times weekly on 3 consecutive days per week • TMP-SMX 75/375 mg/ m^2 body surface area per dose twice daily by mouth every day • TMP-SMX 75/375 mg/m^2 body surface area per dose twice daily by mouth TIW on alternate days	**Primary Prophylaxis Indicated for:** *IgG Antibody to Toxoplasma and Severe Immunosuppression:* • HIV-infected children aged <6 years with CD4 percentage <15%; HIV infected children aged ≥6 years with CD4 count <100 cells/mm^3 **Criteria for Discontinuing Primary Prophylaxis:** Note: Do not discontinue in children aged <1 year • After ≥6 months of cART, and • Aged 1 to <6 years; CD4 percentage is ≥15% for >3 consecutive months • Aged ≥6 years; CD4 count >200 cells/mm^3 for >3 consecutive months **Criteria for Restarting Primary Prophylaxis:** • Aged 1 to <6 years with CD4 percentage <15% • Aged ≥6 years with CD4 count <100 to 200 cells/mm^3
Secondary Prophylaxis (Suppressive Therapy)	• Sulfadiazine 42.5–60 mg/ kg body weight per dose twice daily* (maximum 2–4 g per day) by mouth, plus • Pyrimethamine 1 mg/kg body weight or 15 mg/ m^2 body surface area (maximum 25 mg) by mouth once daily, plus • Leucovorin 5 mg by mouth once every 3 days	• Clindamycin 7–10 mg/kg body weight per dose by mouth 3 times daily, plus • Pyrimethamine 1 mg/kg body weight or 15 mg/ m^2 body surface area (maximum 25 mg) by mouth once daily, plus • Leucovorin 5 mg by mouth once every 3 days **Children Aged 1–3 Months and >24 Months:** • Atovaquone 30 mg/kg body weight by mouth once daily • Leucovorin, 5 mg by mouth every 3 days • TMP-SMX, 150/750 mg/ m^2 body surface area once daily by mouth **Children Aged 4–24 Months:** • Atovaquone 45 mg/kg body weight by mouth once daily, with or without pyrimethamine 1 mg/kg body weight or 15 mg/ m^2 body surface area (maximum 25 mg) by mouth once daily, plus • Leucovorin, 5 mg by mouth every 3 days • TMP-SMX, 150/750 mg/ m^2 body surface area once daily by mouth	**Secondary Prophylaxis Indicated:** • Prior toxoplasmic encephalitis Note: Alternate regimens with very limited data in children. TMP-SMX only to be used if patient intolerant to other regimens **Criteria for Discontinuing Secondary Prophylaxis If All of the Following Criteria are Fulfilled:** • Completed ≥6 months of cART, completed initial therapy for TE, asymptomatic for TE, **and** • Aged 1 to < 6 years; CD4 percentage ≥15% for >6 consecutive months • Aged ≥6 years; CD4 cell count >200 cells/ mm^3 for >6 consecutive months **Criteria For Restarting Secondary Prophylaxis:** • Aged 1 to <6 years with CD4 percentage <15% • Aged ≥6 years with CD4 cell count <200 cells/mm^3
Treatment	**Congenital Toxoplasmosis:**	**For Sulfonamide-Intolerant Patients:**	**Treatment Duration:**

	• Pyrimethamine loading dose—2 mg/kg body weight by mouth once daily for 2 days, then 1 mg/kg body weight by mouth once daily for 2–6 months, then 1 mg/kg body weight by mouth 3 times weekly, plus • Leucovorin (folinic acid) 10 mg by mouth or IM with each dose of pyrimethamine, plus • Sulfadiazine 50 mg/kg body weight by mouth twice daily **Acquired Toxoplasmosis Acute Induction Therapy (Followed by Chronic Suppressive Therapy):** • Pyrimethamine: loading dose—2 mg/kg body weight (maximum 50 mg) by mouth once daily for 3 days, then 1 mg/kg body weight (maximum 25 mg) by mouth once daily, plus • Sulfadiazine 25–50 mg/kg body weight (maximum 1–1.5 g/dose) by mouth per dose 4 times daily, plus • Leucovorin 10–25 mg by mouth once daily, followed by chronic suppressive therapy **Treatment Duration (Followed by Chronic Suppressive Therapy):** • ≥6 weeks (longer duration if clinical or radiologic disease is extensive or response in incomplete at 6 weeks)	• Clindamycin 5–7.5 mg/kg body weight (maximum 600 mg/dose) by mouth or IV per dose given 4 times a day can be substituted for sulfadiazine combined with pyrimethamine and leucovorin	• 12 months **<u>Congenital Toxoplasmosis:</u>** • For infants born to mothers with symptomatic Toxoplasma infection during pregnancy, empiric therapy of the newborn should be strongly considered irrespective of the mother's treatment during pregnancy. **<u>Acquired Toxoplasmosis:</u>** • Pyrimethamine use requires CBC monitoring at least weekly while on daily dosing and at least monthly while on less than daily dosing. • TMP-SMX—TMP 5 mg/kg body weight plus SMX 25 mg/kg body weight per dose IV or by mouth given twice daily has been used as an alternative to pyrimethamine-sulfadiazine in adults but has not been studied in children. • Atovaquone (for adults, 1.5 g by mouth twice daily—double the prophylaxis dose) in regimens combined with pyrimethamine/ leucovorin, with sulfadiazine alone, or as a single agent in patients intolerant to both pyrimethamine and sulfadiazine, has been used in adults, but these regimens have not been studied in children. • Azithromycin (for adults, 900– 1,200 mg/day, corresponding to 20 mg/ kg/day in children) has also been used in adults combined with pyrimethamine-sulfadiazine, but has not been studied in children. • Corticosteroids (e.g., prednisone, dexamethasone) have been used in children with CNS disease when CSF protein is very elevated (>1,000 mg/dL) or there are focal lesions with significant mass effects, with discontinuation as soon as clinically feasible. • Anticonvulsants should be administered to patients with a history of seizures and continued through the acute treatment; but should not be used prophylactically.
*Note: Sulfadiazine may be given as 2–4 equal doses per day as long as the total daily dose is 85–120 mg/kg body weight. **Key to Acronyms**: cART = combination antiretroviral therapy; CBC = complete blood count; CD4 = CD4 T lymphocyte; CNS = central nervous system; CSF = cerebrospinal fluid; IgG = Immunoglobulin G; IM = intramuscular; IV = intravenous; TE = toxoplasmic encephalitis; TMP-SMX = trimethoprim-sulfamethoxazole			

III. Table 3. Recommendations for prevention (prophylaxis) of *Pneumocystis jiroveci* pneumonia in adults and adolescents with HIV[2]

Indication	Preferred regimen	Alternative regimens	Treatment duration
Preventing First Episode of PCP (Primary Prophylaxis)	• TMP-SMX 1 DS tablet PO daily, or • TMP-SMX 1 SS tablet daily	• TMP-SMX 1 DS PO three times weekly, or • Dapsone 100 mg PO daily or 50 mg PO BID, or • Dapsone 50 mg PO daily with (pyrimethamine 50 mg plus leucovorin 25 mg) PO weekly, or • (Dapsone 200 mg plus pyrimethamine 75 mg plus leucovorin 25 mg) PO weekly; or • Aerosolized pentamidine 300 mg via Respigard II™ nebulizer every month, or • Atovaquone 1500 mg PO daily, or • (Atovaquone 1500 mg plus pyrimethamine 25 mg plus leucovorin 10mg) PO daily	• CD4 count increased from <200 cells/ mm^3 to ≥200 cells/mm3 for ≥3 months in response to ART • Can consider when CD4 count is 100–200 cells/ mm^3 and HIV RNA remains below limit of detection of the assay used for ≥3 months to 6 months **Indication for Restarting Primary Prophylaxis:** • CD4 count <100 cells/ mm^3 regardless of HIV RNA • CD4 count 100–200 cells/mm^3 and HIV RNA above detection limit of the assay used
Preventing Subsequent Episode of PCP (Secondary Prophylaxis)	• TMP-SMX 1 DS tablet PO daily, or • TMP-SMX 1 SS tablet daily	• TMP-SMX 1 DS tablet PO three times weekly, or • Dapsone 100 mg PO daily, or • Dapsone 50 mg PO twice daily, or • Dapsone 50 mg PO daily with (pyrimethamine 50 mg plus leucovorin 25 mg) PO weekly, or • (Dapsone 200 mg plus pyrimethamine 75 mg plus leucovorin 25 mg) PO weekly, or • Aerosolized pentamidine 300 mg via Respigard II™ nebulizer every month, or • Atovaquone 1500 mg PO daily with food, or • (Atovaquone 1500 mg plus pyrimethamine 25 mg plus leucovorin 10 mg) PO daily	• CD4 count increased from 200 cells/ mm^3 for >3 months as a result of ART, or • Can consider if CD4 count is 100–200 cells/ mm^3 and HIV RNA remains below limits of detection of assay used for ≥3 months to 6 months • For patients in whom PCP occurs at a CD4 count >200 cells/ mm^3 while not on ART, discontinuation of prophylaxis can be considered once HIV RNA levels are suppressed to below limits of detection of the assay used for ≥3 months to 6 months, although there are no data to support recommendations in this setting. Note: If an episode of PCP occurs at a CD4 count >200 cells/ mm^3 while a patient is on ART, it would be prudent to continue PCP prophylaxis for life, regardless of how high the CD4 cell count rises as a consequence of ART. **Indications for Restarting Secondary Prophylaxis:** • CD4 count <100 cells/ mm^3regardless of HIV RNA • CD4 count 100-200 cells/ mm^3 and HIV RNA above detection limit of the assay used
Note: Patients who are receiving pyrimethamine/sulfadiazine for treatment or suppression of toxoplasmosis do not require additional PCP prophylaxis Key to acronyms = ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; DS = double strength; IV = intravenously; PCP = Pneumocystis pneumonia; PO = orally; SS = single strength; TMP = trimethoprim; TMP-SMX = trimethoprim-sulfamethoxazole			

IV. Table 4. Dose recommendations for the prevention and treatment of cystoisoporiasis in adults and adolescents with HIV[2]

Indication	Preferred regimen	Alternative regimens	Treatment duration
Acute cystoisoporiasis therapy infection	• TMP-SMX (160 mg/800 mg) PO (or IV) QID for 10 days, or • TMP-SMX (160 mg/800 mg) PO (or IV) BID for 7–10 days • One approach is to start with TMP-SMX (160 mg/800 mg) BID regimen first, and increase daily dose and/or duration (up to 3–4 weeks) if symptoms worsen or persist • IV therapy for patients with potential or documented malabsorption	For Patients with Sulfa Intolerance: • Pyrimethamine 50–75 mg PO daily + leucovorin 10–25 mg PO daily, or • Ciprofloxacin 500 mg PO BID for 7 days	7- 10 days
Chronic Maintenance Therapy (Secondary Prophylaxis)	In Patients with CD4 Count <200/mm3: • TMP-SMX (160 mg/800 mg) PO 3 times weekly	• TMP-SMX (160 mg/800 mg) PO daily, or • TMP-SMX (320 mg/1600 mg) PO 3 times weekly, or • Pyrimethamine 25 mg PO daily + leucovorin 5–10 mg PO daily, or • Ciprofloxacin 500 mg PO 3 times weekly as a second line alternative	Sustained increase in CD4 count >200 cells/mm3 for >6 months in response to ART and without evidence of active infection
Key to Acronyms: ART = antiretroviral therapy; BID = twice daily; IV = intravenous; PO = orally; QID = four times a day; TMP-SMX = trimethoprim-sulfamethoxazole			

V. Table 5. Dose recommendations for the prevention and treatment of cystoisoporiasis in HIV-Exposed and HIV-Infected Children[3]

Indication	Preferred regimen	Alternative regimens	Treatment duration / Comments
Primary prophylaxis	There are no U.S. recommendations for primary prophylaxis of isosporiasis.		
Secondary prophylaxis	If Severe Immunosuppression: • Administer TMP-SMX 2.5 mg/kg body weight of TMP component twice daily by mouth 3 times per week	Pyrimethamine 1 mg/kg body weight (maximum 25 mg) plus folinic acid, 10–25 mg by mouth once daily. Second-Line Alternative: • Ciprofloxacin, 10–20 mg/kg body weight given twice daily by mouth 3 times per week	Consider discontinuing secondary prophylaxis in a patient receiving cART after sustained improvement from severe immunosuppression (from CDC immunologic category 3 to CD4 values that fall within category 1 or 2) for longer than 6 months. In adults, the dose of pyrimethamine for secondary prophylaxis (25 mg daily) is lower than the dose for treatment (50–75 mg daily), but no similar data exist for children. Thus, the recommended dosing for secondary prophylaxis in children is 1 mg/kg per dose (maximum 25 mg) once daily. Ciprofloxacin is generally not a drug of first choice in children due to increased incidence of adverse events, including events related to joints and/or surrounding tissues.
Treatment	TMP-SMX 5 mg/kg body weight of TMP component given twice daily by mouth for 10 days	Pyrimethamine 1 mg/kg body weight plus folinic acid 10-25 mg by mouth once daily for 14 days Second-Line Alternatives: • Ciprofloxacin 10–20 mg/kg body weight/day twice daily by mouth for 7 days • Nitazoxanide for 3 consecutive days	If symptoms worsen or persist, the TMPSMX dose may be increased to 5 mg/kg/day given 3–4 times daily by mouth for 10 days or the duration of treatment may be lengthened. Duration of treatment with pyrimethamine has not been well established. Ciprofloxacin is generally not a drug of first choice in children due to increased incidence of adverse events, including events related to joints and/or surrounding tissues.
Key to Acronyms: CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; cART = combination antiretroviral therapy; TMP-SMX = trimethoprim-sulfamethoxazole			

References

1. Daraprim [package insert]. New York, NY: Vyera Pharmaceuticals, LLC; August 2017.
2. Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/whats-new.
3. Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Department of Health and Human Services. Available at https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-pediatric-opportunistic-infections/whats-new.
4. National Cancer Institute. Immunosuppression. Accessed June 16, 2021. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/immunosuppression?redirect=true
5. Centers for Disease Control and Prevention. Malaria Treatment (United States) (Guidelines for Clinicians). Accessed May 21, 2021: https://www.cdc.gov/malaria/diagnosis_treatment/treatment.html
6. Centers for Disease Control and Prevention. Parasites – Toxoplasmosis (toxoplasma infection) (Resources for Health Professionals). Accessed May 21, 2021: https://www.cdc.gov/parasites/toxoplasmosis/health_professionals/index.html#tx
7. Rajapakse S, Weeratunga P, Rodrigo C, de Silva NL, Fernando SD. Prophylaxis of human toxoplasmosis: a systematic review. *Pathog Glob Health*. 2017;111(7):333-342. doi:10.1080/20477724.2017.1370528
8. Maldonado YA, Read JS, COMMITTEE ON INFECTIOUS DISEASES. Diagnosis, Treatment, and Prevention of Congenital Toxoplasmosis in the United States. Pediatrics. 2017 Feb;139(2):e20163860. doi: 10.1542/peds.2016-3860. PMID: 28138010.
9. Green H, Paul M, Vidal L, Leibovici L. Prophylaxis of Pneumocystis pneumonia in immunocompromised non-HIV-infected patients: systematic review and meta-analysis of randomized controlled trials. *Mayo Clin Proc.* 2007;82: 1052-1059.
10. Konstantinovic N, Guegan H, Stäjner T, Belaz S, Robert-Gangneux F. Treatment of toxoplasmosis: Current options and future perspectives [published correction appears in Food Waterborne Parasitol. 2020 Dec 15;21:e00105]. Food Waterborne Parasitol. 2019;15:e00036. Published 2019 Apr 1. doi:10.1016/j.fawpar.2019.e00036
11. Derouin F, Pelloux H. Prevention of toxoplasmosis in transplant patients. *Clinical Microbiology and Infection*. 2008;14(12):1089-1101.
12. Gold Standard, Inc. Pyrimethamine (daraprim) Monograph. Clinical Pharmacology [database online]. Available at: https://www.cms.gov/Medicare/Coverage/CoverageGenInfo/downloads/covdoc17.pdf. Accessed: June 4, 2021.
13. Centers for Disease Control and Prevention (CDC). Parasites – cystoisoporiasis (formerly known as isosporiasis). Last reviewed May 21, 2020. Accessed June 1, 2021. https://www.cdc.gov/parasites/cystoisospora/health_professionals/index.html
14. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant.* 2009;15(10):1143-1238.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated criteria to policy format; Added initial and renewal length of authorization; Added toxoplasmosis prophylaxis, toxoplasmosis treatment, congenital toxoplasmosis, *Pneumocystis jiroveci* pneumonia prophylaxis, and cystoisoporiasis treatment intervention criteria for compound, generic, and brand product; Added brand Daraprim requirement; Added supporting evidence and dosing appendix.	06/2021
Policy created	02/2016

Policy Type: PA/SP Pharmacy Coverage Policy: UMP284

Split Fill Management*

Description

Quizartinib (Vanflyta) is an orally administered selective type II FLT3 inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
quizartinib (Vanflyta)	Acute myeloid leukemia, newly diagnosed, FLT3 mutation-positive, in combination with 7+3 induction and cytarabine consolidation	17.7 mg tablets	60 tablets/30 days
		26.5 mg tablets	60 tablets/30 days

Initial Evaluation

I. **Quizartinib (Vanflyta)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   C. A diagnosis of **Newly diagnosed acute myeloid leukemia (AML)** when the following are met:
      1. The member has FLT3-ITD mutation-positive AML; **AND**
      2. Medication will not be used in combination with any other oncolytic medication with the exception of the therapies outlined below:
         i. Standard 7+3 induction (cytarabine and daunorubicin/idarubicin)
         ii. Cytarabine consolidation therapy; **AND**
      3. The member has received no prior therapy for AML

II. Quizartinib (Vanflyta) is considered investigational when used for all other conditions, including but not limited to:
   A. Acute myeloid leukemia in the absence of FLT3 mutation
   B. Quizartinib (Vanflyta) in combination with oncolytic therapies other than induction and consolidation chemotherapies
   C. Relapsed/ refractory acute myeloid leukemia (R/R AML)
   D. Myelodysplastic syndrome (MDS)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **OR**
    - Member has been established on induction therapy via an inpatient setting; **AND**
        i. Provider attests that the member initiated quizartinib (Vanflyta) as part of standard 7+3 induction therapy (cytarabine and daunorubicin/idarubicin) for AML; **AND**
        ii. Quizartinib (Vanflyta) will be used in combination with cytarabine consolidation therapy; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Member has exhibited improvement or stability of disease symptoms [e.g., achieved complete remission (CR)].

Supporting Evidence

I. Quizartinib (Vanflyta) is a selective type II FLT3 inhibitor studied in combination with chemotherapy as a once daily oral tablet for the treatment of *FLT3*-ITD-positive acute myeloid leukemia (AML). The efficacy and safety of quizartinib (Vanflyta) has not been established in pediatric patients.

II. An estimated 25% of newly diagnosed AML cases have *FLT3*-ITD mutations which are associated with a higher rate of relapse and poorer clinical outcomes as compared to wild type *FLT3* and *FLT*-TKD mutations. However, long-term impact of *FLT3*-ITD mutations on AML prognosis remains unclear. Given the complexities related to diagnosis treatment and management of AML, treatment in this disease space must be initiated by or in consultation with a specialist, such as an oncologist or hematologist.

III. Intensive induction therapy [e.g., cytarabine and an anthracycline (7+3) in combination with midostaurin (Rydapt)] followed by post-remission consolidation therapy [high dose cytarabine (HiDAC) + midostaurin (Rydapt)] and/or allogenic HCT (allo-HCT) in eligible patients has been the standard of care in FLT3-mutated AML. Post induction and consolidation, NCCN recommends maintenance therapy with an FLT3 inhibitor.

IV. Quizartinib (Vanflyta) was studied in a randomized, multi-center, double-blind, placebo-controlled, phase 3 trial of 539 patients with newly diagnosed FLT3-ITD mutated AML (QuANTUM-First). Trial participants (N=539) aged 20 to 75 were randomized 1:1 to receive either a standard 7 + 3 induction therapy with quizartinib (Vanflyta) or placebo, followed by consolidation with HiDAC plus quizartinib (Vanflyta) or placebo, and/or allo-HCT. This was then followed by maintenance with single agent quizartinib (Vanflyta) or placebo.

V. The efficacy of quizartinib (Vanflyta) was assessed via overall survival and event free survival (EFS) endpoints. Overall survival in the ITT population was longer with quizartinib (Vanflyta) than placebo (31·9 months, 95% CI 21·0 – NE vs 15·1 months,13·2 – 26·2; HR 0·774, 0·614 – 0·975; p=0·032). In the population censored for allo-HCT OS also favored quizartinib (Vanflyta) (20·8 months, 95% CI 14·3 – 28·9 vs 12·9 months, 9·2 – 14·7; HR 0·752, 0·75, 0·56–1·01; p=0.055). The key secondary endpoint of EFS per the FDA's definition was not statistically significant (p= 0.24). However, per original protocol with a 56-day cutoff the results did gain statistical significance. In

the induction treatment failure (ITF) population not achieving CRc remission by the end of induction up to day 56 quizartinib (Vanflyta) was found to be 11.9 months (8·1 – 16·5) as compared to 5.7 months (0·3 – 3·42) in the placebo group (HR 0·72, 95% CI 0·592 – 0·897; pnominal=0·0031). Median duration of complete remission was longer with quizartinib (Vanflyta) than with placebo (38·6 months, 95% CI 21·9–NE vs 12·4 months, 8·8–22·7; HR 0·62, 0·45–0·86) and in patients with complete remission during induction, relapse-free survival was longer with quizartinib (Vanflyta) compared to placebo (39·3 months, 95% CI 22·6–NE vs 13·6 months, 9·7–23·7; HR 0·61, 0·44–0·85).

VI. The quality of evidence is considered moderate. The clinical trial program for quizartinib (Vanflyta) consisted of a well-designed randomized clinical trial reporting positive results in overall survival, median duration of complete remission, and median relapse-free survival compared to intensive induction and consolidation therapies alone. However, protocol changes that shifted the definition of EFS may impact the FDA's review of quizartinib (Vanflyta). The effect of allo-HCT on OS and role of long-term quizartinib (Vanflyta) maintenance therapy after chemotherapy has yet to be fully reported. It is unknown how quizartinib (Vanflyta) will compare with other FDA approved medications in the newly diagnosed FLT3-mutated AML population.

VII. All trial participants experienced mild to moderate adverse events (AE) with similar AE profile between arms as both groups received 7 + 3 induction and HiDAC consolidation therapies. The most common AEs reported for quizartinib (Vanflyta) vs placebo included febrile neutropenia (44% vs 42%), pyrexia (42% vs 41%), diarrhea (37% vs 35%), hypokalemia (35% vs 36%), and nausea (34% vs 31%). Distinguishable side effects included QTc prolongation in 14% of the quizartinib (Vanflyta) patients vs 4% in the placebo group.

VIII. Quizartinib (Vanflyta) treatment led to a 34% dose interruption rate in clinical trials and a 19% dose reduction rate due to intolerable AEs. Dose reductions due to QTc prolongation were seen in 4% of quizartinib (Vanflyta) patients. Adverse events associated with a fatal outcome occurred in 30 participants (11%) in the quizartinib (Vanflyta) group and 26 (10%) in the placebo group, infections being the most common cause. Two patients (0.8%) treated with quizartinib (Vanflyta) had a cardiac arrest, with recorded ventricular fibrillation in the setting of severe hypokalemia.

IX. The use of quizartinib (Vanflyta) has not been studied in combination with medications other than 7 + 3 induction and consolidation chemotherapies. Due to lack of safety and efficacy data with a combination regimen, these agents should not be used together.

Investigational or Not Medically Necessary Uses

I. Quizartinib (Vanflyta) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Acute myeloid leukemia in the absence of FLT3 mutation
   B. Quizartinib (Vanflyta) in combination with oncolytic therapies other than induction and consolidation chemotherapies
   C. Relapsed/ refractory acute myeloid leukemia (R/R AML)
   D. Myelodysplastic syndrome (MDS)

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified*

medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.

References

1. Erba HP, Montesinos P, Kim HJ, et al. Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First): a randomised, double-blind, placebo-controlled, phase 3 trial [published online ahead of print, 2023 Apr 25]. Lancet. 2023;S0140-6736(23)00464-6.
2. National Comprehensive Cancer Network. Acute Myeloid Leukemia. NCCN. April 5, 2023. Accessed May 5, 2023. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf.
3. Induction therapy for acute myeloid leukemia in medically-fit adults. UpToDate. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed May 5, 2023. https://www.uptodate.com/
4. Vanflyta. Package insert. Daiichi Sankyo Company, Ltd.; 2023.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
midostaurin (Rydapt®)	Acute myeloid leukemia, newly diagnosed, FLT3 mutation-positive, in combination with cytarabine/daunorubicin induction and cytarabine consolidation
Multi-Targeted Tyrosine Kinase Inhibitors (Multi-TKI)	Unresectable Liver Carcinoma
	Advanced Renal Cell Carcinoma
	Locally Recurrent or Metastatic Progressive Thyroid Cancer
	Advanced Soft Tissue Sarcoma
	Recurrent, High-risk or Metastatic Endometrial Carcinoma
gilteritinib (XOSPATA®)	Relapse/Refractory FLT3 AML

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	08/2023

Policy Type: PA/SP Pharmacy Coverage Policy: UMP020

Description
Obizur is an antihemophilic factor indicated for the treatment of bleeding episodes in adults with acquired hemophilia. Obizur is not indicated for the treatment of congenital hemophilia A or von Willebrand disease.

Length of Authorization
- Initial: 6 months
- Renewal: 6 months

Quantity limits

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit
Obizur, antihemophilic factor (recombinant), porcine sequence	500 units	**Treatment of bleeding episodes in adults with acquired hemophilia A:** • Minor and moderate: Loading dose of 200 IU/kg, followed by maintenance dose titrated to maintain recommended factor VIII trough levels at 50-100 IU/dL every four to 12 hours • Major: Minor and moderate: Loading dose of 200 IU/kg, followed by maintenance dose titrated to maintain recommended factor VIII trough levels at 100-200 IU/dL (to treat acute bleed) every four to 12 hours, then 50-100 IU/dL (after acute bleed is controlled) every four to 12 hours	**Treatment of bleeding episodes in adults with acquired hemophilia A:** Up to the number of doses requested every 28 days

Initial Evaluation

I. Obizur may be considered medically necessary when the following criteria below are met:
   A. Member has a confirmed diagnosis of **acquired hemophilia A (acquired factor VIII deficiency)** when the following are met:
      1. Treatment is prescribed by or in consultation with a hematologist; **AND**
      2. Diagnosis of acquired factor VIII deficiency has been confirmed by blood coagulation testing; **AND**
      3. Used as treatment of bleeding episodes; **AND**
      4. Obizur is not being used for congenital hemophilia A or von Willebrand disease

II. Obizur is considered investigational when used for congenital hemophilia or von Willebrand disease, or any other condition.

Renewal Evaluation

I. Documentation of clinical benefit, including decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline

Supporting Evidence

I. Acquired inhibitors of coagulation are antibodies that either inhibit the activity or increase the clearance of a clotting factor. The most common autoantibodies that affect clotting factor activity and lead to a bleeding disorder are directed against, and interfere with, the activity of factor VIII. This condition is also called acquired hemophilia.
II. Obizur is a recombinant, B domain-deleted porcine (pig) factor VIII indicated for the treatment of patients with autoantibodies to factor VII (i.e. patients with an acquired factor VIII inhibitor). It is not approved for use in patients with congenital (i.e. inherited) hemophilia A.
III. The safety and efficacy of Obizur was established in a small prospective study in patients with an acquired factor VIII inhibitor and severe bleeding. Obizur controlled bleeding in 86% of patients.

Investigational or Not Medically Necessary Uses

There is no evidence to support the use of Obizur in any other condition.

References

1. Obizur® [Prescribing Information]. Lexington, MA: Baxalta; September 2017
2. National Hemophilia Foundation. MASAC Recommendations Concerning products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. Available from: https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations/MASAC-Recommendations-Concerning-Products-Licensed-for-the-Treatment-of-Hemophilia-and-Other-Bleeding-Disorders. Accessed July 5, 2019.
3. UpToDate, Inc. Aquired inhibitors of coagulation. UpToDate [database online]. Last updated June 19, 2019.

Policy Implementation/Update:

Date Created	August 2019
Date Effective	August 2019
Last Updated	August 2019
Last Reviewed	08/2019

Action and Summary of Changes	Date
New policy created for Obizur	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP150

Description

Regorafenib (Stivarga) is an orally administered kinase inhibitor acting on various membrane-bound and intracellular kinases.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
regorafenib (Stivarga)	Gastrointestinal stromal tumor, locally advanced, unresectable or metastatic disease after treatment with imatinib and sunitinib; Colorectal cancer, metastatic, previously treated with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy, an anti-VEGF therapy, and if RAS wild type an anti-EGFR therapy; Hepatocellular (liver) carcinoma, previously treated with sorafenib	40 mg tablets	84 tablets/28 days

Initial Evaluation

I. **Regorafenib (Stivarga)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   C. Medication is **not** used in combination with any other oncolytic medication (i.e., used as monotherapy); **AND**
   D. A diagnosis of one of the following:
      1. **Colorectal Cancer**; **AND**
         i. The member has metastatic (stage IV) disease; **AND**
         ii. The member has previously progressed on or after a chemotherapy regimen history of all of the following:
            a. fluoropyrimidine [e.g., capecitabine, fluorouracil (5-FU)]
            b. oxaliplatin
            c. irinotecan-containing chemotherapy; **AND**

iii. The member has previously progressed on or after an anti-VEGF therapy [e.g., bevacizumab (Avastin)]; **AND**
iv. The member has KRAS-mutated colorectal cancer; **OR**
a. If KRAS wild-type, the member has been treated with an anti-EGFR therapy [e.g., cetuximab (Erbitux), panitumumab (Vectibix)]; **OR**

2. **Gastrointestinal Stromal Tumor**; **AND**
i. The member has locally advanced (stage III), unresectable or metastatic (stage IV) disease; **AND**
ii. The member has previously progressed on or after imatinib (Gleevec); **AND** The member has previously progressed on or after sunitinib (Sutent); **OR**

3. **Hepatocellular Carcinoma; AND**
i. Provider attests the patient has Child-Pugh class A; **AND**
ii. The member has previously progressed on or after sorafenib (Nexavar)

II. Regorafenib (Stivarga) is considered investigational when used for all other conditions, including but not limited to:
A. Biliary cancer, cholangiocarcinoma
B. Esophagogastric cancer (esophageal, gastroesophageal, gastric)
C. Non-small cell lung cancer
D. Renal cell carcinoma
E. Soft tissue sarcoma
F. Adenoid cystic carcinoma
G. Urothelial carcinoma
H. Ovarian cancer
I. Osteosarcoma

Renewal Evaluation

I. Member has received a previous prior authorization for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Regorafenib (Stivarga) will **not** be used in combination with other oncolytic medications (i.e., will be used as monotherapy); **AND**
IV. Documentation of clinical response to therapy, such as stabilization of disease or decrease in tumor size or spread.

Supporting Evidence

I. Regorafenib (Stivarga) has not been evaluated in patients under the age of 18; therefore, its safety and efficacy in the pediatric population is unknown.
II. Due to the complex nature of treating any of the diagnoses regorafenib (Stivarga) is approved for, treatment should be prescribed by, or in consultation with, an oncologist.

III. Regorafenib (Stivarga) was evaluated in a randomized (2:1), double-blind, placebo-controlled study, the CORRECT trial, in adults with metastatic colorectal cancer after failure of standard therapy. The trial included 760 subjects, 505 in the regorafenib arm and 255 in the placebo arm, that had been previously treated with fluoropyrimidine-, oxaliplatin, and irinotecan-based chemotherapy, as well as bevacizumab (Avastin). All but one subject with KRAS wild-type disease received ANTI-EGFR therapy [cetuximab (Erbitux), panitumumab (Vectibix)]. Regorafenib (Stivarga) showed a statistically significant improvement in overall survival (OS) compared to placebo [6.4 months vs. 5 months; HR 0.77 (CI 0.64-0.94), *p* 0.0102].

IV. The safety and efficacy of regorafenib (Stivarga) for gastrointestinal stromal tumors (GIST) was evaluated in a randomized (2:1), double-blind, placebo-controlled trial (GRID) in adults with unresectable, locally advanced or metastatic disease. A total of 199 patients, 133 in the regorafenib arm and 66 in the placebo arm, had been previously treated with imatinib (Gleevec) and sunitinib (Sutent). The medication showed a statistically significant improvement in progression-free survival (PFS) [PFS was 4.8 vs. 0.9 months; HR 0.27 (0.19-0.39), p<0.0001]; however, there was no statistical difference in OS. This may have been influenced by cross-over to active therapy after disease progression on placebo as patients were allowed to change to regorafenib after progression and 56 of the 66 patients moved to the treatment arm.

V. The clinical safety and efficacy of regorafenib (Stivarga) was evaluated in a randomized (2:1), double-blind, placebo-controlled trial (RESORCE) in adults with hepatocellular carcinoma, Child-Pugh class A. All subjects (379 in the regorafenib arm and 194 in the placebo, 573 total) had documented disease progression on sorafenib (Nexavar), and those that had discontinued sorafenib (Nexavar) due to toxicity rather than disease progression were ineligible for the trial; thus, safety and efficacy with regorafenib (Stivarga) prior to progression on or after sorafenib (Nexavar) has not been established. Overall survival was the primary outcome and was statistically significant in favor of regorafenib (Stivarga) over placebo [10.6 vs. 7.8 months; HR 0.63 (0.5-0.79), p<0.0001].

VI. In the clinical trials, severe drug-induced liver injury with fatal outcomes did occur. In the CORRECT study, fatal hepatic failure occurred in 1.6% of patients in the regorafenib arm and in 0.4% of patients in the placebo arm. In the GRID study, fatal hepatic failure occurred in 0.8% of patients in the regorafenib arm. In the RESORCE study, there was no increase in the incidence of fatal hepatic failure as compared to placebo. These drug-induced injuries were typically high-grade elevation of bilirubin, AST, ALT, and ALP with risk of developing injury roughly two-fold in the regorafenib arms compared to placebo.

VII. As regorafenib was only studied in Child-Pugh class A (patients in the lower risk/best survival chances), safety of regorafenib in patients with Child-Pugh class B7 or beyond is unknown with the possibility of drug toxicity with worsening overall outcomes. Additionally, a clinical outreach to a key opinion leader (KOL) specializing in the treatment of liver cancer, agreed that use of regorafenib should be considered after failure of sorafenib, and only in patients with Child-Pugh class A liver status, as they have the best outcomes for a favorable prognosis while balancing the risk of treatment-induced hepatotoxicity. Additionally, the KOL expert noted that the best approach to the management of HCC patients with Child-Pugh class B7 or beyond may be via clinical trial enrollment or a liver transplant.

VIII. For all indications regorafenib (Stivarga) is dosed at 160 mg per day on days 1-21 of each 28-day cycle. Product availability is 40 mg tablets and for patients experiencing dose-dependent

intolerance (adverse reactions), the dose of regorafenib (Stivarga) should be reduced in 40mg increments, with the lowest recommended dose of 80mg/day.

Investigational or Not Medically Necessary Uses

I. Regorafenib (Stivarga) has not been sufficiently studied for safety or efficacy and/or is currently being evaluated in clinical trials for the following indications:
   A. Osteosarcoma
      i. First-line therapy for osteosarcoma is surgically removing the tissue/bone involved (either limb-sparing or limb-amputation) with radiation therapy followed by chemotherapy - based on the type and affected site of osteosarcoma (chondrosarcoma, Ewing sarcoma, Giant Cell Tumor of bone, etc.). Recommended systemic therapy options in this setting are: pembrolizumab (Keytruda), dasatinib (Sprycel), pazopanib (Votrient) or cisplatin/doxorubicin or MAP (high-dose methotrexate, cisplatin, and doxorubicin).
      ii. The NCCN panel updated guidelines to give regorafenib a category 1 recommendation for second-line therapy for osteosarcoma (relapsed, refractory, or metastatic disease), based on the following data of two phase 2 clinical trials (REGOBONE and SARC024) noting that regorafenib displayed antitumor activity in progressive metastatic osteosarcoma, delaying disease progression. However, at this time, regorafenib has not received FDA approval for the treatment of osteosarcoma.
      iii. In the REGOBONE study, the primary endpoint was the number of patients without disease progression at 8 weeks. Patients were randomly assigned 2:1 to regorafenib or placebo with 38 patient total in the end efficacy analysis. 17 of 26 patients in the regorafenib arm (65%) were non-progressive at 8 weeks compared with 0 patients in the placebo arm. Although a preliminary indicator of efficacy, these results were not statistically significant, neither the study powered to evaluate the difference between the treatment and placebo arms.
      iv. In the SARC024 (randomized, double-blind, phase 2 study), progression free survival (PFS) was the primary endpoint. SARC024 had 42 patients randomized 1:1 to regorafenib or placebo with allowance of crossover at time of disease progression. Median PFS was significantly improved with regorafenib versus placebo: 3.6 months (95% CI, 2.0 to 7.6 months) versus 1.7 months (95% CI, 1.2 to 1.8 months), respectively (hazard ratio, 0.42; 95% CI, 0.21 to 0.85; *p* 0.017). In the context of the crossover design, there was no statistically significant difference in overall survival. Additionally, based on consensus recommendations from the clinical experts, a progression-free survival (PFS) of ≥ 4months has been regarded as a clinically meaningful metric of positive outcomes in the setting of osteosarcoma, which this trial did not attain.
   B. Biliary cancer, cholangiocarcinoma
   C. Esophagogastric cancer (esophageal, gastroesophageal, gastric)
   D. Non-small cell lung cancer
   E. Renal cell carcinoma

F. Soft tissue sarcoma
G. Adenoid cystic carcinoma
H. Urothelial carcinoma
I. Ovarian cancer

References

1. Stivarga [Package Insert]. Whippany NJ. Bayer Healthcare Pharmaceuticals Inc. 2017. Revised 12/2020.
2. Wihelm SM., Dumas J., Adnane L., et al. Regorafenib: a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer. 2011;129(1): 245-255).
3. Van Cutsem E., Sobrero AF., Siena S., et al. Phase III CORRECT trial of regorafenib in metastatic colorectal cancer (mCRC). J Clin Oncol. 2012: 2502.
4. Grothey A, Van Cutsem E, Sobrero A, et. al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013 Jan;381(9863):303-12.
5. Bruix, J, Qin, S, Merle, P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017 Jan 07;389(10064):56-66.
6. Demetri GD, Reichardt P, Kang Y-K, et. al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013 Jan;381(9863):295-302.
7. Grothy A., Sobrero AF., Siena S., et al. Results of a phase III randomized, double-blind, placebo-controlled, multicenter trial (CORRECT) or regorafenib plus best supportive care versus placebo in patients with metastatic colorectal cancer who have progressed after standard therapies.
8. NCCN Clinical Practice Guidelines in Oncology- Color Cancer Version 1.2022 Available at : https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf Accessed 3/2022
9. NCCN Clinical Practice Guidelines in Oncology: Gastrointestinal Stromal Tumors (GISTs) Version 1.2022. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1507
10. NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancers Version 5.2021 Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1438
11. Duffaud F, Mir O, Boudou-Rouquette P, Piperno-Neumann S; French Sarcoma Group. Efficacy and safety of regorafenib in adult patients with metastatic osteosarcoma: a non-comparative, randomised, double-blind, placebo-controlled, phase 2 study. Lancet Oncol. 2019 Jan;20(1):120-133. doi: 10.1016/S1470-2045(18)30742-3. Epub 2018 Nov 23. PMID: 30477937
12. Davis LE, Bolejack V, Ryan CW, Ganjoo KN, et al. Randomized Double-Blind Phase II Study of Regorafenib in Patients With Metastatic Osteosarcoma. J Clin Oncol. 2019 Jun 1;37(16):1424-1431. doi: 10.1200/JCO.18.02374. Epub 2019 Apr 23. PMID: 31013172; PMCID: PMC7799443.

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Related Policies

Policy Name	Disease state
Avapritinib (Ayvakit)	Unresectable or metastatic gastrointestinal stromal tumor with PDGFRA exon 18 mutation
Cabozantinib (Cabometyx, Cometriq)	Progressive or metastatic hepatocellular carcinoma, in patients previously treated with sorafenib
Dasatinib (Sprycel)	Gastrointestinal Stromal Tumors (GIST)
Encorafenib (Braftovi), binimetinib (Mektovi)	Metastatic colorectal cancer, with BRAF V600E mutation, combination therapy
Ripretinib (Qinlock)	Gastrointestinal Stromal Tumor, advanced disease after treatment with three or more tyrosine kinase inhibitors
Sunitinib (Sutent)	Gastrointestinal stromal tumor

Trifluridine/tipiracil (Lonsurf)	Colorectal cancer-metastatic, previously untreated
Multi-Targeted Tyrosine Kinase Inhibitors (Multi-TKI)	Unresectable hepatocellular carcinoma

Policy Implementation/Update:

Action and Summary of Changes	Date
Added in Child-Pugh class A to hepatocellular cancer requirement based on KOL, NCCN, and clinical trial recommendations. Updated supporting evidence for the three FDA indications.	08/2022
Removed split fill	01/2022
Prior authorization transitioned to policy format. Addition of age edit, addition of monotherapy requirement. Renewal criteria transitioned to current formatting and language and increase from three to 12 month approval.	11/2019
Previous Reviews	01/2013; 02/2013; 04/2014; 09/2014;

Policy Type: PA/SP Pharmacy Coverage Policy: UMP228

Description

Relugolix is an orally administered gonadotropin-releasing hormone (GnRH) antagonist.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
relugolix (Orgovyx)	120 mg tablets	Prostate cancer	**Initial**: 30 tablets/28 days for one month **Maintenance**: 30 tablets/30 days

Initial Evaluation

I. **Relugolix (Orgovyx)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist or urologist; **AND**
   C. A diagnosis of **prostate cancer**; **AND**
      1. Provider attestation the member is castration sensitive; **AND**
      2. Prostate cancer is advanced or metastatic (Stage III or IV); **AND**
      3. Treatment with a GnRH agonist (e.g., leuprolide [Lupron]), has been ineffective, not tolerated, or all GnRH agonists are contraindicated; **OR**
         i. The member has a history of a major adverse cardiovascular event (MACE) (e.g., myocardial infarction, stroke); **AND**
      4. Degarelix (Firmagon) has been ineffective, not tolerated, or is contraindicated; **AND**
   D. Relugolix (Orgovyx) is medically necessary for the treatment of prostate cancer over GnRH agonists and degarelix (Firmagon) [documentation of medically necessity is verified by a clinical pharmacist at the health plan]. (Note – preference for oral administration or other convenience does not meet medical necessity)

II. Relugolix is considered investigational when used for all other conditions, including but not limited to:
   A. Castration-resistant prostate cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If so, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
    A. Documentation of disease response to treatment (e.g., stabilization of disease or decrease in tumor size or tumor spread, reduction in serum testosterone or PSA); **OR**
    B. Provider attestation that continuation of therapy is necessary if the member has had disease progression

Supporting Evidence

I. Relugolix (Orgovyx) is a gonadotropin-releasing hormone (GnRH) receptor antagonist, FDA-approved for the treatment advanced prostate cancer. A 360 mg loading dose (three tablets) is administered on day one, then a maintenance dose of 120 mg (one tablet) is taken once daily. It is one of several androgen deprivation therapies (ADT) available. Other options include GnRH agonists such as leuprolide (Lupron), goserelin (Zoladex), triptorelin (Telstar/Triptodur), histrelin (Supprelin LA, Vantas), and GnRH agonist [degarelix (Firmagon)], all of which are injectable medications. Additionally, surgical orchiectomy is an option when prompt castration is required. Reducing serum testosterone to castrate levels is warranted for the treatment of prostate cancer, and all of these methods are highly effective. Androgen deprivation therapy is a hallmark of treatment, and is generally continued, if tolerated, even if there is progressive disease and/or if other prostate cancer medications are started. Given the specialization of the condition and treatment options, therapy should be prescribed by, or in consultation with, an oncologist.
II. The GnRH agonists are highly utilized for the treatment of advanced or metastatic prostate cancer. They are known to cause a testosterone surge upon initiation, with a subsequent decrease in serum testosterone three-to-four weeks after starting treatment. For patients at risk for these symptoms, an antiandrogen therapy (e.g., flutamide, nilutamide, bicalutamide) may be administered concurrently for the first few weeks of GnRH agonist treatment. Some agents are available in every-three-month injections and are generally well tolerated
III. The GnRH antagonists, degarelix (Firmagon), and now relugolix (Orgovyx), are successful at mitigating the testosterone surge and may rapidly reduce testosterone; although, the rapidity of testosterone suppression with GnRH antagonists has not been linked to superior clinical benefit over the GnRH agonists in the general population likely to utilize these therapies.
IV. Relugolix (Orgovyx) was evaluated in one Phase 3, randomized, open-label, non-inferiority (NI) trial vs. leuprolide (Lupron) over 48 weeks in patients with advanced or metastatic disease. Up to 13% of patients had previous ADT, 30% had previous radiotherapy, and 14% had a history of major adverse cardiovascular event (MACE). There was a washout period of three months for those previously treated with degarelix (Firmagon) and one year for those on GnRH agonist therapy. Those with a MACE in the six months before the trial were excluded. All patients included in the trial were adults, which is the expected population to be diagnosed with prostate

cancer. At this time the safety and efficacy of relugolix (Orgovyx) in pediatric patients remains unknown; however, it would be very rare for a pediatric patient to develop prostate cancer.

V. The primary outcome was cumulative sustained castration rate of less than 50 ng/dL from day 29 through 48 weeks. Results were 96.7% of patients for relugolix (Orgovyx) and 88.8% for leuprolide (Lupron), with a difference of 7.9% (CI 4.1-11.8). Additionally, a notable secondary outcome was castration relapse free survival (CRFS) at 48 weeks. This was 74% for relugolix (Orgovyx) and 75% for leuprolide (Lupron) (HR 1.03, CI 0.68-1.57, p=0.84). Both of these outcomes showed NI of relugolix (Orgovyx) to leuprolide (Lupron). Statistically, relugolix (Orgovyx) was superior to leuprolide (Lupron) in the primary outcome; however, both therapies showed a very high rate of sustained castration. At this time definitive data are lacking to indicate clinical superiority of either product in regard to medication efficacy.

VI. There were several other secondary outcomes measured: probability of testosterone suppression to less than 50 ng/dL on day four and day 15, prostate specific antigen (PSA) response on day 15 and day 29, probability of profound testosterone suppression (less than 20 ng/dL) on day 15. These were all superior for relugolix (Orgovyx) over leuprolide (Lupron). This is expected given the mechanistic differences of the therapies. Given the known initial testosterone surge with GnRH agonists, castrate levels would be expected three-to-four weeks after medication initiation. The results confirm the rapidity of testosterone suppression for relugolix (Orgovyx), as expected for a GnRH antagonist.

VII. Rate of overall adverse events (AE) was consistent across both groups. Common AE (greater than 10%) that occurred in both groups included laboratory abnormalities, increase glucose levels, increase triglycerides, musculoskeletal pain, increased hemoglobin, ALT/AST increases, constipation, and diarrhea.

VIII. Serious AE occurred in 9.8% of the relugolix (Orgovyx) group, and 15.3% of the leuprolide (Lupron) group. For relugolix (Orgovyx) sAE: myocardial infarction (0.8%), AKI (0.6%), hemorrhage (0.6%), and UTI (0.5%).

IX. The MACE rate was 2.9% for relugolix (Orgovyx) and 6.2% for leuprolide (Lupron), overall. This was further pronounced in the subgroup of patients that had a previous MACE. Rates were 3.6% and 17.8%, respectively. In the group without a previous MACE, rates were 2.8% and 4.2%, respectively. From the data, it is predicted that GnRH antagonists may have a favorable safety profile in those with history of a MACE, such as myocardial infarction and stroke. Options include degarelix (Firmagon) as well as relugolix (Orgovyx), and current data are lacking to indicate clinical favorability between these two agents.

Investigational or Not Medically Necessary Uses

I. Relugolix has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Castration-resistant prostate cancer

References

1. Shore N., Saad F., Cookson M., et al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. *N Engl J Med.* 2020;382(23):2187-2196.
2. Orgovyx [Prescribing Information]. Myovant Sciences, Inc. Brisbane, CA. December 2020.
3. National Comprehensive Cancer Network, NCCN Guidelines. Prostate Cancer. V.3.2020. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx. Updated November 17, 2020.
4. PDQ Adult Treatment Editorial Board. PDQ Prostate Cancer Treatment. Bethesda, MD: National Cancer Institute. Updated December 10, 2020. Available at: https://www.cancer.gov/types/prostate/hp/prostate-treatment-pdq. Accessed January 25, 2021 [PMID: 26389471]
5. Lowrance WT, Breau RH, Chou R et al: Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline PART I and II. J Urol 2021; 205: 14, 22.
6. Firmagon [Prescribing Information]. Ferring Pharmaceuticals. Parisppany, NJ. February 2015.
7. Lupron Depot [Prescribing Information]. Abbvie Inc. Chicago, IL. January 2019.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy

Policy Name	Disease state
GnRH Antagonists in Gynecologic Conditions	Heavy menstrual bleeding associated with uterine fibroids (leiomyoma) Moderate to severe pain associated with endometriosis
Gonadotropin-releasing hormone (GnRH)	Endometriosis, Central Precocious Puberty (CPP), Advanced Prostate Cancer, Uterine leiomyoma (fibroids), Advanced breast cancer in premenopausal women, Reduction of endometrial thickness prior to endometrial ablation, Gender Dysphoria

Policy Implementation/Update:

Action and Summary of Changes	Date
Myfembree moved to GnRH Antagonists in Gynecologic Conditions policy for uterine fibroids and moderate to severe pain with endometriosis; Endometriosis removed from E/I section; Changed policy name to relugolix (Orgovyx)	11/2022
Policy created	05/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP117

Description

Repository corticotropin injection (Acthar, Cortrophin) gel is an adrenocorticotropic hormone (ACTH) analogue that stimulates the adrenal cortex to secrete cortisol, corticosterone, aldosterone, and other weak androgenic substances.

Length of Authorization

- Initial: One month
- Renewal: One month, total of two courses allowed per lifetime (i.e., one renewal allowed).

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
repository corticotropin injection (Acthar Gel)	Infantile Spasms (West Syndrome)	80 units/mL vial (400 units/5mL)	Monthly quantity in mL to allow for: 150 u/m^2 daily for two weeks plus a two-week taper as follows: three days' worth of 30 u/m^2, three days' worth of 15 u/m^2, six days' worth of 10 u/m^2
repository corticotropin injection (Purified Cortrophin Gel)			

Initial Evaluation

I. **Repository corticotropin (Acthar Gel)** may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a neurologist; **AND**
   B. A diagnosis of one of **Infantile Spasms (West Syndrome)**; **AND**
      1. Member is under two years of age; **AND**
      2. Medication to be used as monotherapy; **AND**
      3. Documentation of recent body surface area; **OR**
         i. Documentation of member's height and weight (needed for dose calculation).; **OR**

II. **Repository corticotropin (Purified Cortrophin Gel)** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above have been met; AND
      1. Documentation that treatment with repository corticotropin injection (Acthar Gel) has been ineffective, not tolerated, or contraindicated.

III. Repository corticotropin (Acthar Gel) and Repository corticotropin (Purified Cortrophin Gel) are considered not medically necessary when criteria above are not met and/or when used for the following:

A. Multiple sclerosis
B. Rheumatoid arthritis
C. Psoriatic arthritis
D. Ankylosing spondylitis
E. Dermatomyositis/polymyositis
F. Optic neuritis (40 units daily, also included in investigational section for other doses, see below)
G. For use in nephrotic syndrome over corticosteroid therapy (also included in investigational section, see below)

IV. Repository corticotropin (Acthar Gel) and Repository corticotropin (Purified Cortrophin Gel) are considered investigational when used for all other conditions, including but not limited to:
A. In combination with anti-epileptic therapies for the treatment of infantile spasms (West Syndrome)
B. Ophthalmic conditions and diseases: keratoconjunctivitis sicca, Sjogren's syndrome, dry eye disease, keratitis, iritis, iridocyclitis, uveitis, choroiditis, optic neuritis, etc.
C. Nephrotic syndrome (NS) and NS due to focal segmental glomerulosclerosis (FSGS) or immunoglobulin A nephropathy (IgAN)
D. Juvenile rheumatoid arthritis
E. Lupus erythematosus
F. Dermatologic conditions: erythema multiforme, Steven's Johnson syndrome
G. Serum sickness
H. Sarcoidosis

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. A diagnosis of one of **Infantile Spasms (West Syndrome)**; **AND**
    A. Member is under two years of age; **AND**
    B. Medication to be used as monotherapy; **AND**
    C. Documentation of recent body surface area; **OR**
        a. Documentation of member's height and weight (needed for dose calculation); **AND**
IV. The member has been previously treated successfully with an initial treatment course of repository corticotropin (Acthar, Cortrophin) gel (i.e., improvement in seizures); **AND**
V. The member has relapsed, and a second course of therapy is warranted; **AND**
VI. The member has not yet received a total of two or more courses of therapy in their lifetime.

Supporting Evidence

I. **Infantile spasms (West Syndrome):** Repository corticotropin (Acthar) gel is an ACTH analogue that acts similarly to corticosteroids and was FDA-approved for infantile spasms in 2010. Data from several randomized controlled trials are available to support safety and efficacy. One clinical trial showed superiority over prednisone in the proportion of patient responders to therapy. Other studies directly comparing therapy to corticosteroids did not determine statistical superiority of repository corticotropin (Acthar) gel. Although data for superiority of repository corticotropin (Acthar) gel over corticosteroids are conflicting, there is insufficient evidence to support that corticosteroids could be more effective than repository corticotropin (Acthar) gel. Guidelines recommend repository corticotropin (Acthar) as the mainstay therapy.

- Infantile spasms are characterized as epileptic spasms that appear in infancy and early childhood. The majority of patients will present before seven months of age, and the condition is associated with electroencephalographic pattern of hypsarrhythmia. This medication has been evaluated and is only FDA-approved for patients under two years of age. In patients older than two years, alternative cost-effective treatment options should be considered.
- In clinical practice, repository corticotropin (Acthar) gel has been utilized at a variety of doses. The FDA-approved dose (which has also been evaluated in several clinical trials) is as follows: 150 units/m^2 daily (divided between twice daily) for two weeks plus a two-week taper: three days each of 30 units/m^2, 15 units/m^2, 10 units/m^2, followed by 10 units/m^2 every other day for six days. The last six days of therapy equates to total of three additional days of 10 units/m^2 (equating to six full days of the 10 units/m^2 dose). Several studies have evaluated differing dosing regimens, including lower doses. In the event under dosing is prescribed relative to the FDA-approved dose, this regimen should be allowed given some evidence to indicate that lower doses may be as effective as that FDA-approved. Repository corticotropin (Acthar) gel has been evaluated in clinical trials using 150 units/m^2 for three weeks then a taper for three more weeks; however, this higher dose group did not show superior efficacy to lower doses. Similar rates of response and relapse occurred; thus, at this time there is no evidence to support need for a longer than two-week duration of 150 units/m^2 per day.
- Duration of initial therapy with treatment and taper is four weeks. Response is expected in the first few weeks. There is lack of evidence to support extended use of therapy; however, a second course of therapy may be appropriate for patients that relapse and require retreatment. Lack of response (i.e., number/severity of spasms) on first treatment course signals an alternative regimen should be utilized for retreatment; thus, response to the initial therapy course is required. Long-term safety is similar to corticosteroids: cardiac, ocular, mood, sleep, skin concerns, etc.
- Repository corticotropin (Cortrophin) gel is not FDA-approved for the indication of infantile spasms; however, is not expected to have any clinical differences. This is a more cost-effective treatment option, and when other criteria are met for the indication of infantile spasms, Cortrophin use is covered under the specifications listed above (e.g., QLL, etc.). ANI Pharmaceuticals received FDA-approval of Purified Cortrophin gel in November 2021, in efforts to support broader and more cost-effective access to corticotropin products.

II. Repository corticotropin (Acthar) gel was FDA-approved in 1952 and Cortrophin gel was approved in 1954 for the treatment of inflammatory conditions prior to current FDA standards, and the indications were grandfathered into the labels; however, corticotropin products have not demonstrated evidence for safety and efficacy, or medical necessity over corticosteroids, for the majority of the labeled indications. Furthermore, the cost has increased significantly over the past few decades: $36 per vial in 2001; in 2022, $49,750 per vial for Acthar and $38,200 for Cortrophin. The evidence for indications outside of infantile spasms and multiple sclerosis (MS) are absent, are low quality and/or lacking ability to conclude efficacy and safety alone or in comparison to more cost-effective therapies (e.g., corticosteroids). Data to support efficacy for indications other than infantile spasms are absent from the prescribing information label. The manufacturer of Acthar, Mallinckrodt has funded several Phase 4 clinical trials in recent years in efforts to provide support for the approved indications; however, by in large these clinical trials are insufficient to support the safety and efficacy and/or medical necessity over other therapies.

Investigational or Not Medically Necessary Uses

I. Repository corticotropin (Acthar, Cortrophin) (ACTH) gel is considered not medically necessary for the following conditions:
   A. Multiple sclerosis: At this time, it is unproven if ACTH gel is more likely to provide similar therapeutic results or is superior to other corticosteroids, given lack of quality trials and trials with consistent results showing superiority; however, ACTH gel is more costly than other therapies that could be utilized. Given these factors ACTH gel is not medically necessary for MS and is not covered. Furthermore, choice of or success of therapy in acute MS exacerbation has not been correlated with improved or superior long-term outcomes, further reducing the necessity of ACTH gel for this condition.
   B. Rheumatoid arthritis, psoriatic arthritis, dermatomyositis/polymyositis, ankylosing spondylitis: ACTH gel has been evaluated in Phase 4, randomized, placebo-controlled withdrawal studies for these conditions in addition to several lesser quality trials. In some trials, therapy was superior to placebo for disease response; however, this medication has not been directly compared to NSAIDS, the majority of systemic corticosteroids, conventional synthetic DMARDs, specialty DMARDS, and biologic therapies. Numerous other medications have strong evidence for safety and efficacy, all of which are more cost-effective. At this time, it is unproven if ACTH gel is more likely to produce similar therapeutics results or is superior to other therapies; however, ACTH gel is more costly than other therapies that could be utilized. Furthermore, ACTH gel is not recognized as an appropriate therapy per guidelines or standard practice; thus, is considered not medically necessary and is not covered.
   C. Optic neuritis (also considered experimental and investigational, see below): ACTH gel was evaluated in one RCT vs. placebo, where 40 units daily for 30 days did not provide significant changes over placebo in visual acuity and visual field scores. Given that it is not known if therapy improves therapeutic outcomes at this dose, ACTH gel is considered not medically necessary and is not covered.

D. Nephrotic syndrome: superiority of ACTH gel over corticosteroids and other treatment options for this condition has not been demonstrated; certain trials have shown lack of benefit over placebo therapy and one clinical trial showed noninferiority to methylprednisolone. At this time, it is unproven if ACTH gel is more likely to provide similar therapeutic results or is superior to other corticosteroid therapies; however, ACTH gel is more costly than other therapies that could be utilized. Given these factors ACTH gel is not medically necessary and is not covered.

II. Repository corticotropin (Acthar, Cortrophin) gel has not been sufficiently studied for safety and efficacy, and are considered experimental and investigational, for the following conditions or settings below:
    A. In combination with anti-epileptic therapies for the treatment of infantile spasms (West Syndrome): ACTH gel has only been evaluated as monotherapy for the treatment of infantile spasms. There is unknown safety and efficacy when utilized for other anti-epileptic medications. When combination therapy is indicated vigabatrin plus corticosteroids may be considered as available evidence for efficacy and safety.
    B. Systemic lupus erythematosus (SLE): Evaluated in a single-arm, open-label, four-week trial in 10 patients. This trial does not provide any certainty in the benefit of ACTH gel for SLE given the significant trial biases: subjective outcomes in an open-label trial, no comparator to be able to determine extent of benefit over placebo (if any), few patients evaluated, and concomitant medications which may have impacted/influenced the changes.
    C. Optic neuritis (ON) (higher doses): Evaluated in a single-arm, open-label, 2-week trial at a starting dose of 80 units daily in 24 patients with ON. This trial does not provide any certainty in the benefit of therapy for ON given the significant biases in the trial: subjective outcomes in an open-label trial, few patients evaluated, short trial duration, and patients were on background therapies at the start of the trial, with no washout period. Results/conclusions seen in this assessment may not be attributable to ACTH gel.
    D. Sarcoidosis: Evaluated for sarcoidosis in one retrospective medical record review, on provider assessment of “patients’ health status”. The trial showed that use of concomitant medications such as glucocorticoids decreased with use of ACTH gel. This trial does not provide any certainty in the benefit of therapy for this condition given the significant biases: retrospective trial design, subjective and invalidated outcomes in a nonblinded trial, most patients were on background therapies. Results/conclusions seen in this assessment may not be attributable to ACTH gel.
    E. Nephrotic Syndrome (NS), including but not limited to those with FSGS: Evaluated in retrospective case series; a prospective, open-label, single arm trial, a randomized noninferiority trial vs. methylprednisolone with cytotoxic therapies; a randomized, placebo-controlled trial; a dose comparison trial; and one Cochrane systematic review evaluated in one retrospective case series in 44 patients (15 patients had FSGS). Data are heavily conflicting, none of which strongly point to medication benefit. For example, one of the randomized controlled trials showed no substantial differences compared to no therapy and the trial was ended early for no benefit. In the noninferiority trial, similar responses were seen to methylprednisolone. The Cochrane review determined lack of sufficient data to draw conclusions of efficacy and safety. The collection of data does not provide certainty of benefit of therapy for NS, is considered experimental and

investigational, and is not covered by the health plan. At this time, it is also unproven if ACTH gel is more likely to provide similar therapeutic results or is superior to other corticosteroid therapies; however, ACTH gel is more costly than other therapies that could be utilized. Thus, ACTH gel is also not medically necessary over corticosteroids and is not covered.

i. NS due to immunoglobulin A nephropathy (IgAN): ACTH gel was evaluated in a single-arm, open-label pilot study in 19 patients. This trial does not provide any certainty in the benefit of therapy for this condition given the significant biases in the trial, including but not limited to small number of patients in the trial, lack of comparator arm, and the majority of outcomes were unchanged at follow-up.

F. Ophthalmic conditions and diseases, including but not limited to: keratoconjunctivitis sicca, Sjogren's syndrome, dry eye disease, keratitis, iritis, iridocyclitis, uveitis, choroiditis:

i. Keratitis/dry eye disease: ACTH gel was evaluated in a single-arm, open-label study in 35 patients with keratitis. The trial observed 12-point change in IDEEL score for 17 patients (50%) with severe keratitis. ACTH gel was also evaluated in a single-arm, open-label pilot study in dry eye disease in 15 patients. The study evaluated the SANDE questionnaire for patient reported improvement; however, these trials do not provide any certainty in the benefit of therapy for this condition given the significant biases in the trial, including but not limited to subjective outcomes in an open-label trial, lack of comparator, the small number of patients evaluated, and background or concomitant therapies may not have been reported so any results or conclusions may not be attributable to ACTH gel. Furthermore, the SANDE score is not a validated measurement tool for clinically meaningful change in dry eye comfort or symptom improvement.

1. Alternative therapies and management strategies include, but may not be limited to: avoidance of offending medications, environmental management, moisture conserving eyewear, ocular lubricants, artificial tears and preservative-free artificial tears (gels, ointments, drops), ophthalmic cyclosporine (generic, Restasis, Cequa), ophthalmic lifitegrast (Xiidra), nasal varenicline (Tyrvaya), punctal plugs or occlusion, topical steroids, therapeutic contact lenses, autologous serum tear preparations.

ii. Uveitis: ACTH gel has been evaluated for uveitis in one retrospective trial evaluating medical record data of provider assessment on patients' health status for 91 patients. Trial conclusions were that provider reported improved patient status; however, this trial does not provide any certainty in the benefit of therapy for this condition given the significant biases in the trial, including but not limited to subjective outcomes in an open-label trial, lack of comparator, the small number of patients evaluated, and background or concomitant therapies were utilized by 100% of patients (including steroid eye drops, oral steroids, intraocular steroids, and non-steroid eye drops) so any results or conclusions may not be attributable to ACTH gel.

III. Juvenile rheumatoid arthritis
IV. Dermatologic conditions: erythema multiforme, Steven's Johnson syndrome
V. Serum sickness

VI. Sarcoidosis

Appendix

I. Methods to calculate body surface area include, but are not limited to the Mosteller method: BSA (m^2) = Square root ((Ht (cm) x Wt (kg))/3600)

References

1. Acthar Gel [Prescribing Information]. Mallinckrodt ARD LLC. Bedminster, NJ. October 2021.
2. Purified Cortrophin Gel [Prescribing Information]. ANI Pharmaceuticals, Inc. Baudette, MN. November 2021.
3. Tran KA, Harrod C, Bourdette DN, Cohen DM, Deodhar AA, Hartung DM. Characterization of the clinical evidence supporting repository corticotropin injection for fda-approved indications: a scoping review. JAMA Intern Med. 2022;182(2):206-217.
4. Baram TZ, Mitchell WG, Tournay A, Snead OC, Hanson RA, Horton EJ. High-dose corticotropin (Acth) versus prednisone for infantile spasms: a prospective, randomized, blinded study. Pediatrics. 1996;97(3):375-379.
5. Hrachovy RA, Frost JD, Glaze DG. High-dose, long-duration versus low-dose, short-duration corticotropin therapy for infantile spasms. The Journal of Pediatrics. 1994;124(5):803-806.
6. Go CY, Mackay MT, Weiss SK, et al. Evidence-based guideline update: medical treatment of infantile spasms: report of the guideline development subcommittee of the american academy of neurology and the practice committee of the child neurology society. Neurology. 2012;78(24):1974-1980.
7. Nelson GR. Management of infantile spasms. Transl Pediatr. 2015;4(4):260-270.
8. National Multiple Sclerosis Society. Managing Relapses. Available at: https://www.nationalmssociety.org/Treating-MS/Managing-Relapses#section-2
9. Multiple Sclerosis Association of America. Treating Multiple Sclerosis Relapse. October 2017. Available at: https://mymsaa.org/ms-information/treatments/relapses/
10. Barnes MP, Bateman DE, Cleland PG, et al. Intravenous methylprednisolone for multiple sclerosis in relapse. Journal of Neurology, Neurosurgery & Psychiatry. 1985;48(2):157-159.
11. Milanese C, Mantia LL, Salmaggi A, et al. Double-blind randomized trial of acth versus dexamethasone versus methylprednisolone in multiple sclerosis bouts. ENE. 1989;29(1):10-14.
12. Thompson AJ, Kennard C, Swash M, et al. Relative efficacy of intravenous methylprednisolone and ACTH in the treatment of acute relapse in MS. Neurology. 1989;39(7):969-969.
13. Prevoo MLL, Van'T Hof MA, Kuper HH, Van Leeuwen MA, Van De Putte LBA, Van Riel PLCM. Modified disease activity scores that include twenty-eight-joint counts development and validation in a prospective longitudinal study of patients with rheumatoid arthritis: MODIFIED DISEASE ACTIVITY SCORE. Arthritis & Rheumatism. 1995;38(1):44-48.
14. Fiechtner JJ, Montroy T, June J. A single-site, investigator initiated open-label trial of H.P. Acthar® Gel (repository corticotropin injection) an adrenocorticotropic hormone (ACTH) analogue in subjects with moderately to severely active psoriatic arthritis (PsA). J Dermatol Res Ther. 2016;2(5):1-7.
15. B.P. Wordsworth, M. J. Pearcy, A. G. Mowat, In-patient regime for the treatment of ankylosing spondylitis: an appraisal of improvement in spinal mobility and the effects of corticotrophin. *Rheumatology*. 1984;23(1):39-43.
16. Fleischmann R, Furst DE, Connolly-Strong E, Liu J, Zhu J, Brasington R. Repository corticotropin injection for active rheumatoid arthritis despite aggressive treatment: a randomized controlled withdrawal trial. Rheumatol Ther. 2020;7(2):327-344.
17. Aggarwal R, Marder G, Koontz DC, Nandkumar P, Qi Z, Oddis CV. Efficacy and safety of adrenocorticotropic hormone gel in refractory dermatomyositis and polymyositis. Ann Rheum Dis. 2018;77(5):720-727.
18. Fiechtner JJ, Montroy T. Treatment of moderately to severely active systemic lupus erythematosus with adrenocorticotropic hormone: a single-site, open-label trial. Lupus. 2014;23(9):905-912.
19. Chopra I, Qin Y, Kranyak J, et al. Repository corticotropin injection in patients with advanced symptomatic sarcoidosis: retrospective analysis of medical records. Ther Adv Respir Dis. 2019;13:1753466619888127. doi:10.1177/1753466619888127.

20. Michelle A. Hladunewich, Daniel Cattran, Laurence H. Beck, Ayodele Odutayo, Sanjeev Sethi, Rivka Ayalon, Nelson Leung, Heather Reich, Fernando C. Fervenza, A pilot study to determine the dose and effectiveness of adrenocorticotrophic hormone (H.P. Acthar® Gel) in nephrotic syndrome due to idiopathic membranous nephropathy, Nephrology Dialysis Transplantation, Volume 29, Issue 8, August 2014, Pages 1570–1577
21. Wang C shi, Travers C, McCracken C, et al. Adrenocorticotropic hormone for childhood nephrotic syndrome. CJASN. 2018;13(12):1859-1865.
22. Wirta D, McLaurin E, Ousler G, Liu J, Kacmaz RO, Grieco J. Repository corticotropin injection (Acthar® Gel) for refractory severe noninfectious keratitis: efficacy and safety from a phase 4, multicenter, open-label study. Ophthalmol Ther. 2021;10(4):1077-1092.
23. Grubbs JR, Tolleson-Rinehart S, Huynh K, Davis RM. A review of quality of life measures in dry eye questionnaires. Cornea. 2014;33(2):215-218.
24. Nelson WW, Lima AF, Kranyak J, et al. Retrospective medical record review to describe use of repository corticotropin injection among patients with uveitis in the United States. J Ocul Pharmacol Ther. 2019;35(3):182-188.
25. Bryan MS, Sergott RC. Changes in visual acuity and retinal structures following repository corticotropin injection (RCI) therapy in patients with acute demyelinating optic neuritis: improvement in low contrast visual acuity in both affected and contralateral eyes in a single-armed open-label study. J Neurol Sci. 2019;407:116505. doi:10.1016/j.jns.2019.116505.
26. Alhamad T, Manllo Dieck J, Younus U, et al. ACTH gel in resistant focal segmental glomerulosclerosis after kidney transplantation. Transplantation. 2019;103(1):202-209.
27. Hladunewich MA, Cattran D, Beck LH, et al. A pilot study to determine the dose and effectiveness of adrenocorticotrophic hormone (Acthar® Gel) in nephrotic syndrome due to idiopathic membranous nephropathy. Nephrol Dial Transplant. 2014;29(8):1570-1577.
28. Madan A, Mijovic-Das S, Stankovic A, Teehan G, Milward AS, Khastgir A. Acthar Gel in the treatment of nephrotic syndrome: a multicenter retrospective case series. BMC Nephrol. 2016;17:37.
29. Zand L, Canetta P, Lafayette R, et al. An open-label pilot study of adrenocorticotrophic hormone in the treatment of IgA nephropathy at high risk of progression. Kidney Int Rep. 2020;5(1):58-65.

Related Policies

Currently, there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated criteria to require an inadequate response, intolerance, or contraindication to repository corticotropin (Acthar Gel) prior to repository corticotropin (Purified Cortrophin Gel), effective 10/01/2022	09/2022
Policy criteria updated for infantile spasms indication: removal of congenital infection rule out, addition of body surface (or height and weight) requirement for dose calculation. Change of renewal criteria to check that patients still meet initial requirements and that member has had a response to therapy that would predict response with a retreatment. Criteria updated to allow for maximum of two courses per lifetime. Supporting evidence updated for infantile spasms, not medically necessary and experimental and investigational designations and information added for supporting evidence. Addition of Cortrophin to policy. Formatting updates.	06/2022
Policy created	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP289

Description

Resmetirom (Rezdiffra) is a liver-targeted thyroid hormone receptor-beta (THR-β) selective agonist pending FDA-approval for the treatment of adults with nonalcoholic steatohepatitis (NASH) with liver fibrosis.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
resmetirom (Rezdiffra)	nonalcoholic steatohepatitis (NASH)	For weight < 100kg: 80 mg tablets	30 tablets/30 days
		For weight ≥100kg: 100 mg tablets	

Initial Evaluation

I. **Resmetirom (Rezdiffra)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a hepatologist or gastroenterologist; **AND**
   C. Member has a diagnosis of **nonalcoholic steatohepatitis (NASH)** when the following are met:
      1. Diagnosis is biopsy confirmed; **AND**
      2. Documented liver fibrosis stage F2 or F3; **AND**
      3. Other causes of liver disease or hepatic steatosis have been ruled out (e.g., alcoholic steatohepatitis, acute fatty liver, autoimmune hepatitis, Hepatitis A, B or C, hemochromatosis, drug-induced liver disease, etc.); **AND**
   D. Provider attestation member has adopted liver-protective lifestyle interventions such as optimizing weight loss, dietary changes, and exercise; **AND**
   E. Provider attestation member is optimizing standard of care pharmacologic treatment to manage comorbid diseases, including, but not limited to cardiovascular disease, dyslipidemia, diabetes, hypertension; **AND**
   F. Member does not have evidence of cirrhosis, hepatic decompensation, or hepatocellular carcinoma (HCC)

II. Resmetirom (Rezdiffra) is considered investigational when used for all other conditions, including but not limited to:
   A. Heterozygous Familial Hypercholesterolemia
   B. Evidence of cirrhosis (F4), hepatic decompensation, or hepatocellular carcinoma (HCC)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Disease response to treatment defined by improvement in fibrosis or stabilization/no worsening of fibrosis as determined by non-invasive tests (e.g., transient elastography (e.g., FibroScan), magnetic resonance elastography (MRE), etc.); **AND**
IV. Member has not progressed to cirrhosis, experienced hepatic decompensation events, or hepatocellular carcinoma (HCC)

Supporting Evidence

I. Resmetirom (Rezdiffra) is a liver-targeted thyroid hormone receptor-beta (THR-β) selective agonist for the treatment of adults with nonalcoholic steatohepatitis (NASH) with liver fibrosis. When activated in the liver, THR-β leads to the breakdown of stored fat.
II. Non-alcoholic fatty liver disease (NAFLD) is characterized by an abnormal accumulation of fat in the liver. NAFLD can be subcategorized as nonalcoholic fatty liver (NAFL), in which there is hepatic steatosis (HS) but no injury to liver cells, and as nonalcoholic steatohepatitis (NASH), in which HS is accompanied by hepatocellular injury.
III. NASH can progress to liver fibrosis, and liver fibrosis can progress to irreversible cirrhosis and hepatocellular carcinoma (HCC). NASH and alcoholism are the top two indications for liver transplantations and is the leading indication for liver transplantation in adults 65 years of age and older and women of all ages. NAFLD is closely linked to and often precedes the development of metabolic abnormalities (insulin resistance, dyslipidemia, obesity, and hypertension). Having several metabolic abnormalities confers an even greater risk of histological progression of NASH and all-cause mortality.
IV. In 2023, it was proposed by hepatology medical societies that the naming for these conditions be updated to metabolic-associated fatty liver disease (MAFLD) and metabolic steatohepatitis (MASH).
V. Diagnosis of suspected disease in most patients is based on clinical and laboratory data as well as imaging with appropriate exclusion of other liver conditions, but NASH is also a diagnosis of exclusion, which includes excluding: other causes of hepatic steatosis [alcoholic steatohepatitis, acute fatty liver, autoimmune hepatitis, Hepatitis A, B and C, hemochromatosis, drug-induced liver disease, etc.), absence of coexisting chronic liver disease, and exclusion of significant alcohol consumption.
VI. Abnormal laboratory results indicating liver injury (e.g., aminotransferase levels (AST, ALT, etc.) may be detected and managed by primary care practitioners (PCPs), but should not be

used in isolation to make a definitive NASH diagnosis. Individuals with intermediate to high-risk NASH or cirrhosis should be referred to hepatology or gastroenterology to undergo additional monitoring and confirmatory tests.

VII. Liver biopsy is regarded as the gold standard to diagnose NASH. Several noninvasive testing (NIT) methods to detect fibrosis in patients with liver disease have been established as alternatives to biopsy, however may not provide accurate diagnostic specificity. Degree of steatohepatitis may only be detected with a liver biopsy. When there is diagnostic uncertainty in patients with indeterminate, unreliable, or conflicting NITs, diagnosis via liver biopsy remains the most reliable method to confirm advanced fibrosis and progression of NASH.

VIII. Patients with hepatic steatosis or clinically suspected NAFLD based on the presence of obesity and metabolic risk factors should undergo primary risk assessment with a fibrosis risk stratification by the fibrosis-4 (FIB-4 index), which is a common noninvasive test to help estimate the amount of scarring in the liver. The score calculates age, AST and ALT levels, and platelet count.

IX. The 2023 American Association for the Study of Liver Diseases (AASLD) and 2022 American Association of Clinical Endocrinology (AACE) guidelines provide guidance on the clinical care pathway for initial risk stratification and management of patients with NASH:

a. Low risk of advanced fibrosis is defined as an FIB-4 score < 1.3, LSM < 8.0 kPa by transient elastography (TE) or a liver biopsy fibrosis stage of F0–F1.
b. Intermediate/Indeterminate risk is defined as an FIB-4 score between ≥ 1.3 and 2.67 and/or an LSM between 8.0 and 12.0 kPa on TE, and in those patients who are unable or unwilling to obtain a liver biopsy.
c. High risk is defined as an FIB-4 score > 2.67, LSM > 12.0 kPa by TE, or a liver biopsy that shows clinically significant liver fibrosis (F2–F4).

X. There is no single or specific NIT that is recommended; however, liver-specific imaging, including vibration-controlled transient elastography (VCTE) (e.g., FibroScan®) are commonly used to assess liver stiffness and can be used to exclude significant hepatic fibrosis. VCTE can assess the presence of liver disease through a combination of controlled attenuation parameter (CAP) and liver stiffness measurement (LSM), which assess hepatic fat and liver stiffness, respectively. Changes in liver stiffness may be useful in identifying disease progression. Hepatic fat may also be assessed using magnetic resonance imaging-proton density fat fraction (MRI-PDFF), which determines fat content via the difference in resonance frequencies between fat and water and can additionally quantify steatosis. Other common NITs used in clinical practice include magnetic resonance elastography (MRE), enhanced liver fibrosis test (ELF), and acoustic radiation force impulse imaging (ARFI) (Virtual Touch™ tissue quantification, ElastPQ).

XI. Patients with NASH and at least stage 2 fibrosis (F2), referred to as “at-risk” NASH, have a demonstrably higher risk of liver-related morbidity and mortality.

XII. Lifestyle intervention is the key therapeutic intervention for patients with NAFLD. The American Association for the Study of Liver Diseases (AASLD) guidance on the management of NAFLD endorse dietary modification, increased physical activity, and weight loss. A weight loss of 5% to 10% of body weight can reverse hepatic steatosis and stabilize or diminish NASH in many patients, but this goal is frequently difficult to achieve. AASLD emphasizes

optimizing glucose control for patients with diabetes, lipid-lowering therapy for patients with hyperlipidemia, and abstinence from alcohol for patients with clinically significant hepatic fibrosis.

XIII. Goal of pharmacologic therapy for NASH is to slow the progress of, halt, or reverse fibrosis while patients are still pre-cirrhotic. As of December 2023, resmetirom (Rezdiffra) is anticipated to be the first FDA-approved therapy for NASH. Vitamin E and pioglitazone have been used historically and may improve the histologic changes of NASH, but data are limited. Some of the medications approved for commonly associated comorbidities such as T2DM and obesity have been studied in the context of NASH and may reduce liver enzymes or steatosis or improve liver histology. Therefore, medications with possible liver-related benefits should be optimized when managing comorbidities.

XIV. MAESTRO-NASH is an ongoing randomized, double-blind, placebo-controlled Phase 3 trial in patients with NASH and liver fibrosis. This study incorporates a 52-week serial liver biopsy analysis in 966 patients with biopsy-confirmed NASH and significant fibrosis (stage F1b, F2, F3). Patients were randomly assigned to placebo, resmetirom 80 mg, or resmetirom 100 mg once daily. Baseline characteristics were balanced across treatment arms and include BMI 36 kg/m^2, type 2 diabetes (67%), hypertension (78%), dyslipidemia (71%; LDL 99 mg/dL); baseline liver biopsy nonalcoholic fatty liver disease activity score (NAS) ≥ 5 (84%); baseline fibrosis stage: F3 (62%), F2 (33%), F1B (5%). The NAS is a validated scoring system with scores ranging from 0–8 and are composed of the unweighted sum of semi-quantitative steatosis (0–3), ballooning (0–2), and lobular inflammation scores (0–3).

XV. Dual primary endpoints evaluated the proportion of patients with NASH resolution with at least 2 points reduction in without worsening of fibrosis at least 1 point improvement in the fibrosis stage with no worsening of NAS. Key secondary endpoint included percent change from baseline in LDL-C (after 24 weeks). The 52-week dual primary endpoint and the key secondary endpoint were met for both the 80 mg and 100 mg dose of resmetirom (Rezdiffra). 26% (80 mg) and 30% (100 mg) of patients randomized to resmetirom had NASH resolution without worsening of fibrosis stage compared to 10% of the placebo group ($p < 0.0001$ for both comparisons). Additionally, 24% (80 mg) and 26% (100 mg) of patients randomized to resmetirom had ≥ 1 stage improvement in fibrosis without worsening of NASH compared with 14% for the placebo group ($p < 0.0001$ for both comparisons).

XVI. The onset of adverse events (AEs) were typically observed during the first weeks of treatment, and most treatment-related AEs were considered mild or moderate in severity, and transient. The overall incidence of AE was comparable between treatment groups, with most common AE (>10%) in resmetirom arm being diarrhea, nausea, vomiting, arthralgia, urinary tract infection, and COVID-19 infection. There were no instances of drug induced liver injury (DILI).

XVII. Framework recommendations are based on critical appraisal of the evidence for safety and efficacy and defines clinically meaningful endpoints/benefits inclusive of, but are not limited to morbidity, mortality, symptom control, physical/emotional functioning, and quality of life. Historically, several pharmacologic therapies have been studied for the treatment of patients with NASH, however, most trials have not been able to detect a clinically meaningful difference, had significant safety issues, and/or been too short to determine an impact on important patient-centered clinical outcomes. The quality of evidence is

considered moderate, as resmetirom (Rezdiffra) met both dual primary endpoints and achieved greater rates of stabilization of fibrosis compared to placebo. Fibrosis histology is an accepted surrogate endpoint and one of the strongest predictors for clinical outcomes; however, uncertainty remains regarding the magnitude of the long-term benefits of resmetirom (Rezdiffra). The effects of resmetirom (Rezdiffra) on the ultimate progression of NASH to worsening fibrosis, cirrhosis, and the outcomes of liver failure, need for transplantation, and early mortality cannot be known from this relatively short-term pivotal trial.

XVIII. Data from the MAESTRO-NASH trial will be reinforced by the Phase 3 MAESTRO clinical development program, including the MAESTRO-NASH-OUTCOMES, MAESTRO-NAFLD-1 and MAESTRO-NAFLD-OLE safety clinical trials. Resmetirom (Rezdiffra) was approved under the accelerated approval pathway based on evaluating liver histological improvements predicted to slow the progression of NASH defined as resolution of NASH without worsening fibrosis stage or improvement in fibrosis stage with no worsening of NAS. Continued approval for the treatment of NASH is contingent upon verification and description of clinical benefit in confirmatory trials. The 54-month analysis of MAESTRO-NASH in approximately 1,700 patients is on-going and will include the following endpoints: a composite clinical outcome composed of all-cause mortality, liver transplant, and significant hepatic events (including hepatic decompensation events [ascites, encephalopathy, or variceal hemorrhage], histological progression to cirrhosis, and a confirmed increase of MELD score.

Investigational or Not Medically Necessary Uses

I. Resmetirom (Rezdiffra) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Heterozygous Familial Hypercholesterolemia (HeHF)
      i. Resmetirom (Rezdiffra) was evaluated in a 12-week, double-blind, randomized, placebo-controlled Phase 2 trial in patients with HeFH (NCT03038022). Resmetirom reduced LDL-C levels by 18.8% (95% CI: -27.8% to -9.8%; $P < 0.0001$) compared with placebo at Week 12, with a mean difference of -27 mg/dL (95% CI: -38.4 to -15.5 mg/dL; $P < 0.0001$). Study limitations included small sample size, short treatment and follow-up duration, and inclusion of a homogeneous population. Additional studies are needed to further evaluate the potential role of resmetirom in the management of patients with HeFH.
   B. Cirrhosis, hepatic decompensation, or hepatocellular carcinoma (HCC)
      i. Patients with cirrhosis, patients with prior hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy), or in hepatocellular carcinoma (HCC) were excluded from participating in the MAESTRO-NASH clinical program. Reversal of cirrhosis in these patients may not be feasible and the efficacy and safety of resmetirom in this patient population is unknown.

References

1. Harrison SA, Ratziu V, Anstee QM, et al. Design of the phase 3 MAESTRO clinical program to evaluate resmetirom for the treatment of nonalcoholic steatohepatitis. *Aliment Pharmacol Ther*. 2024;59(1):51-63.
2. Resmetirom preapproval product dossier. Madrigal Pharmaceuticals. September 2023.
3. Juluri R, Vuppalanchi R, Olson J, et al. Generalizability of the nonalcoholic steatohepatitis Clinical Research Network histologic scoring system for nonalcoholic fatty liver disease. *J Clin Gastroenterol*. 2011;45(1):55-58. doi:10.1097/MCG.0b013e3181dd1348
4. Fahim SM, Tice JA, Suh K, et al. Resmetirom for nonalcoholic steatohepatitis. *J Manag Care Spec Pharm*. 2023;29(10):1169-1172. doi:10.18553/jmcp.2023.29.10.1169
5. Center for Drug Evaluation and Research. Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment Guidance for Industry. Updated December 2018. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/noncirrhotic-nonalcoholic-steatohepatitis-liver-fibrosis-developing-drugs-treatment
6. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology*. 2023;77(5):1797-1835.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
obeticholic acid (Ocaliva)	Primary Biliary Cholangitis (PBC)

Policy Implementation/Update

Action and Summary of Changes	Date
Policy created	02/2024

Policy Type: PA Pharmacy Coverage Policy: UMP056

Description

Rifaximin (Xifaxan) is an orally administered rifamycin antibacterial agent that inhibits bacterial RNA synthesis by binding to bacterial DNA-dependent RNA polymerase.

Length of Authorization

- Initial:
  - i. Irritable Bowel Syndrome with Diarrhea (IBS-D): one time approval
  - ii. Hepatic encephalopathy: six months
  - iii. Traveler's diarrhea: one time approval
- Renewal:
  - i. IBS-D: one-time approval, maximum of three fills per lifetime
  - ii. Hepatic encephalopathy: 12 months
  - iii. Traveler's diarrhea: N/A

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
rifaximin (Xifaxan)	550 mg tablets	Treatment of irritable bowel syndrome with diarrhea (IBS-D).	42 tablets/ 14 days	150969, 152498
		Hepatic encephalopathy recurrence.	60 tablets/30 days	
	200 mg tablets	Travelers' diarrhea caused by noninvasive strains of Escherichia coli	9 tablets/3 days	088395, 088393

Initial Evaluation

I. Rifaximin (Xifaxan) may be considered medically necessary when the following criteria below are met:
  A. A diagnosis of one of the following:
    i. **Irritable Bowel Syndrome with Diarrhea (IBS-D)**; **AND**
      a. Member is 18 year of age or older; **AND**
      b. Rifaxamin (Xifaxan) is prescribed by or in consultation with a gastroenterologist; **AND**
      c. Treatment with at least three therapies from different groups have been tried and failed, not tolerated or all are contraindicated (please note, if one or more groups is contraindicated, a trial of three agents from the remaining classes will be required):
        a. Group 1: antidiarrheal (e.g., loperamide, bismuth subsalicylate, diphenoxylate/atropine, paregoric)
        b. Group 2: bile acid sequestrant (e.g., cholestyramine, colestipol)
        c. Group 3: antispasmodic (e.g., dicyclomine, hyoscyamine)

d. Group 4: Tricyclic serotonergic agent: (e.g., amitriptyline, nortriptyline, imipramine, desipramine)

OR

ii. **Traveler's diarrhea**; **AND**
   a. Member is 12 years of age or older; **AND**
   b. Treatment with azithromycin (Zithromax) or a fluoroquinolone (e.g., ciprofloxacin) have been ineffective, not tolerated, or BOTH are contraindicated; **OR**

iii. **Hepatic encephalopathy**; **AND**
   a. Member is 18 year of age or older; **AND (a or b)**
      a. Treatment with lactulose has been ineffective, contraindicated, or not tolerated; **OR**
      b. Rifaxamin (Xifaxan) will be used as add-on treatment

II. Rifaximin (Xifaxan) is considered investigational when used for all other conditions, including but not limited to:
   A. Small Intestinal Bacterial Overgrowth (SIBO)

Renewal Evaluation

I. **Irritable Bowel Syndrome with Diarrhea (IBS-D); AND**
   A. There has been a 10 week treatment-free period since prior approval of rifaximin (Xifaxan); **AND**
   B. The member has not had more than two prior treatments with rifaximin (Xifaxan). A maximum of three approvals is allowed per lifetime for the treatment of IBS-D; **OR**

II. **Hepatic encephalopathy; AND**
   A. Clinical documentation indicating disease stability or improvement.

Supporting Evidence

I. Rifaximin (Xifaxan) is indicated for adults and pediatric patients 12 years of age and older with travelers' diarrhea, and adults older than 18 years of age with hepatic encephalopathy or IBS-D. Infectious Diseases Society of America clinical practice guidelines recommend treatment with fluoroquinolones or azithromycin as first line treatment of travelers' diarrhea.

II. The FDA approved dose is 200 mg three times daily for three days for traveler's diarrhea.

III. The American Association for the Study of Liver Diseases and European Association for the Study of the Liver clinical practice guidelines suggest initial therapy with lactulose for the treatment of hepatic encephalopathy. Rifaximin (Xifaxan) is an effective add-on therapy to lactulose for prevention of recurrence.

IV. Treatment options for IBS-D include antidiarrheals, antibiotics, antispasmodics, antidepressants, and bile acid sequestrants. The American College of Gastroenterology gave moderate or weak recommendations for all IBS-D therapies due to poor quality of evidence and applicability to patient groups. Due to insufficient comparative evidence for efficacy, other treatment options provide a better value over rifaximin (Xifaxan). Of the antidepressants, tricyclic agents have

shown to slow intestinal transit; however, SSRI/SNRI agents have less published data and the data available is inconsistent in showing benefit in IBS.

V. Rifaximin (Xifaxan) will be authorized for a total of three courses per lifetime for IBS-D per FDA label. In clinical studies, 14-day repeat treatment courses were separated by 10 weeks.

Investigational or Not Medically Necessary Uses

I. Small Intestinal Bacterial Overgrowth (SIBO)
   A. Although likely an association exists between IBS-D and SIBO, the evidence linking a causal relationship between the two diagnoses is conflicting.
   B. Intestinal motility disorders and chronic pancreatitis are estimated to account for approximately 90 percent of cases of SIBO. Underlying etiology of SIBO should be addressed prior to pharmacologic therapy. Common causes of SIBO include: anatomic abnormalities; strictures, motility Issues, hypochlorhydria, immunodeficiency, chronic pancreatitis, cirrhosis, end stage renal disease, or medications (e.g., proton pump inhibitors, tricyclic antidepressants, opioids).
   C. Rifaximin (Xifaxan) use in adults with SIBO has not been evaluated in multicenter, prospective, randomized, placebo-controlled trials. Although five single-site, open-label, randomized controlled trials demonstrated a potential modest benefit of rifaximin (Xifaxan) use in adults with a SIBO, the studies were poorly designed, had a small sample size, and had minimal follow up.
   D. Gastroenterological Association Institute clinical guidelines for treatment of SIBO have not been established.

References

1. Xifaxan [package insert]. Raleigh, NC: Salix Pharmaceuticals; May 2015
2. Shane AL, Mody RK, Crump JA, Tarr PI, Steiner TS, Kotloff K, et al. 2017 Infectious Diseases Society of America Clinical Practice Guidelines for the Diagnosis and Management of Infectious Diarrhea. Clin Infect Dis. 2017 Nov 29;65(12):e45-e80. doi: 10.1093/cid/cix669.
3. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, Weissenborn K. et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014 Aug;60(2):715-35. doi: 10.1002/hep.27210. Epub.
4. Weinberg DS, Smalley W, Heidelbaugh JJ, Sultan S; Amercian Gastroenterological Association. American Gastroenterological Association Institute Guideline on the pharmacological management of irritable bowel syndrome. Gastroenterology. 2014 Nov;147(5):1146-8. doi: 10.1053/j.gastro.2014.09.001. Epub 2014 Sep 16.
5. Shah ED, Basseri RJ, Chong K, Pimentel M, Abnormal breath testing in IBS: a meta-analysis. Dig Dis Sci. 2010 Sep;55(9):2441-9. Epub 2010 May 14.
6. Clinical Guidelines (Sortable List. American College of Gastroenterology. Date Accessed: 14, April 2019. http://gi.org/clinical-guidelines/clinical-guidelines-sortable-list/
7. Furnari M, Parodi A, Gemignani L, Giannini EG, Marenco S, Savarino E, et al. Clinical trial: the combination of rifaximin with partially hydrolysed guar gum is more effective than rifaximin alone in eradicating small intestinal bacterial overgrowth. Aliment Pharmacol Ther. 2010 Oct;32(8):1000-6. doi: 10.1111/j.1365-2036.2010.04436.x. Epub 2010 .
8. Scarpellini E1, Giorgio V, Gabrielli M, Filoni S, Vitale G, Tortora A, et al. Rifaximin treatment for small intestinal bacterial overgrowth in children with irritable bowel syndrome. Eur Rev Med Pharmacol Sci. 2013:(10):1314-20.
9. Lauritano EC, Gabrielli M, Lupascu A, Santoliquido A, Nucera G, Scarpellini E, et al. Rifaximin dose-finding study for the treatment of small intestinal bacterial overgrowth. Aliment Pharmacol Ther. 2005 Jul 1;22(1):31-5.
10. Di Stefano M, Malservisi S, Veneto G, Ferrieri A, Corazza GR. Rifaximin versus chlortetracycline in the short-term treatment of small intestinal bacterial overgrowth. Aliment Pharmacol Ther. 2000 May;14(5):551-6.
11. Lauritano EC, Gabrielli M, Scarpellini E, Ojetti V, Roccarina D, Villita A, et al. Antibiotic therapy in small intestinal bacterial overgrowth: rifaximin versus metronidazole. Eur Rev Med Pharmacol Sci. 2009 Mar-Apr;13(2):111-6

Policy Implementation/Update:

Date Created	August 2015
Date Effective	August 2015
Last Updated	July 2019
Last Reviewed	08/2015; 04/2019, 07/2019

Action and Summary of Changes	Date
Criteria for the IBS-d indicated updated to require three prior therapies prior to payment consideration. Additionally, agents with low quality or conflicting data were removed from the list of conventional agents allowed for previous trial and failure. Rearrangement of criteria to include the most requested indication first.	07/2019
Updated to policy format, evidence for the investigational use of rifaximin (Xifaxan) in SIBO updated, addition of specialist involvement in prescribing for IBS-D, age criteria edited.	04/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP214

Description

Riluzole (Rilutek®, Teglutik®, Exervan®) is an orally administered benzothiazole for the treatment of patients with amyotrophic lateral sclerosis (ALS).

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
riluzole (Rilutek) *	50 mg tablet	Amyotrophic lateral sclerosis (ALS)	60 tablets/30 days
riluzole (Teglutik)	50 mg/10 mL (5 mg/mL) oral suspension		600 ml/30 days
riluzole (Exervan)	50 mg film		60 films/30 days

**Generic riluzole* is a formulary agent and does not require prior authorization

Initial Evaluation

I. Riluzole (Rilutek, Teglutik, Exervan) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a neurologist; **AND**
   C. A diagnosis of **Amyotrophic lateral sclerosis (ALS); AND**
   D. Treatment with generic riluzole tablet has been ineffective, contraindicated, or not tolerated.

II. Riluzole (Rilutek, Teglutik, Exervan) are considered investigational when used for all other conditions, including but not limited to:
   A. Treatment-resistant depression
   B. Chorea in Huntington's disease

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise.; **AND**

III. Documentation of clinical benefit, including stabilization of disease and absence of unacceptable toxicity from the drug [e.g. hepatic injury, severe neutropenia, interstitial lung disease]; **AND**
IV. Treatment with generic riluzole tablet has been ineffective, contraindicated, or not tolerated

Supporting Evidence

I. According to the American Academy of Neurology (AAN) two randomized controlled clinical trials and one cross-sectional study, show that multidisciplinary clinics specializing in ALS care are likely effective in several ways, which include improved quality of life and lengthened survival. The AAN guidelines recommend that specialized multidisciplinary clinical referral should be considered for patients with ALS to optimize health care delivery and prolong survival and may be linked to enhanced quality of life.
II. The safety and efficacy of riluzole (Rilutek®) in pediatric patients with amyotrophic lateral sclerosis (ALS) has not been established.
III. According to the American Academy of Neurology (AAN) practice parameter for the care of patients with ALS, riluzole is safe and effective for slowing disease progression to a modest degree in ALS. They therefore recommend that riluzole should be offered to slow disease progression in patients with ALS.

Investigational or Not Medically Necessary Uses

I. In a randomized, double-blind, placebo-controlled sequential trial that evaluated the efficacy and safety of adjunctive riluzole for treatment-resistant major depressive disorder (MDD), 104 participants were randomized in a 2:3:3 ratio to receive riluzole/riluzole, placebo/placebo and placebo/riluzole. The trial had two phases of 4 weeks each, and the primary endpoint was change in depression severity as assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS), which did not show a statistically significant difference between riluzole and placebo.
II. Chorea is a hallmark of Huntington Disease (HD), along with cognitive decline and psychiatric impairment. The AAN guidelines for pharmacologic treatment of HD, notes two randomized controlled trials evaluating riluzole for chorea for HD using different doses (100 mg or 200 mg) and durations (8 weeks and 3 years). The first study (n=63) showed a statistically significant reduction in unified huntington's disease rating scale (UHDRS) in patients who received riluzole 200 mg/day (-2.2 ± 3.3, p 0.01); however, statistical significance was observed in those who received riluzole 100 mg/day [-0.2 ± 2.9; vs placebo (± 0.7 ± 3.4)]. In the second study (n=537), no statistically significant difference in UHDRS chorea scores at 3 years was observed between participants who received riluzole 50 mg twice daily and placebo. Although the guidelines recommend riluzole 200 mg/day with level B of evidence for HD chorea, there is modest evidence on the efficacy and safety of riluzole for chorea in HD.

References

1. Riluzole (Teglutik®) [Prescribing information]. Berwyn, PA: ITF Pharma, Inc. March 2020.
2. Riluzole (Rilutek®) [Prescribing Information]. Switzerland: Covis Pharma. March 2020.

3. Miller RG, Jackson CE, Kasarkis EJ, et al. Practice Parameter update: The care of the patient with
4. amyotrophic lateral sclerosis: Multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review). Neurology® 2009;73:1227–1233.
5. Miller RG, Jackson CE, Kasarkis EJ, et al. Practice Parameter update: The care of the patient with amyotrophic lateral sclerosis: Drug, nutritional, and respiratory therapies (an evidence-based review). . Neurology® 2009;73:1218 –1226.
6. Mathew SJ, Gueorguieva R, Brandt C, et al. A Randomized, Double-Blind, Placebo-Controlled, Sequential Parallel Comparison Design Trial of Adjunctive Riluzole for Treatment-Resistant Major Depressive Disorder. Neuropsychopharmacology (2017) 42, 2567–2574.
7. Armstrong MJ, Miyasaki JM. Evidence-based guideline: Pharmacologic treatment of chorea in Huntington disease. Neurology® 2012;79:597–603.
8. Riluzole (Exervan®) [Prescribing information]. Jersey City, NJ: Mitsubishi Tanabe Pharma America, September 2021.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added Exervan to policy	09/2021
Criteria changed to policy format, added age requirement, specialist referral/prescription, step through generic riluzole tablet and renewal evaluation.	12/2020
Criteria created	07/2013

Policy Type: PA Pharmacy Coverage Policy: UMP207

Description

Ripretinib (Qinlock) is an orally administered tyrosine kinase inhibitor (TKI) that inhibits KIT proto-oncogene receptor tyrosine kinase (KIT) and platelet derived growth factor receptor A (PDGFRA) kinase.

Length of Authorization

I. Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
ripretinib (Qinlock)	50 mg tablets	Gastrointestinal Stromal Tumor, advanced disease after treatment with three or more tyrosine kinase inhibitors, including imatinib	90 tablets/30 days

Initial Evaluation

I. Ripretinib (Qinlock) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. Ripretinib (Qinlock) will be used as monotherapy (i.e., will not be used in combination with any other oncology therapy); **AND**
   D. A diagnosis of **Gastrointestinal Stromal Tumor (GIST)** when the following are met:
      1. Member has advanced (Stage III), unresectable or metastatic (Stage IV) disease; **AND**
      2. Member has previously progressed on, or after, **ALL** of the following:
         a. imatinib (e.g., Gleevec)
         b. sunitinib (Sutent)
         c. regorafenib (Stivarga)

II. Ripretinib (Qinlock) is considered investigational when used for all other conditions, including but not limited to:
   A. Third-line or prior treatment of gastrointestinal stromal tumor
   B. Advanced Systemic Mastocytosis or other hematologic malignancies
   C. Soft Tissue Sarcoma, outside of gastrointestinal stromal tumor
   D. Malignant Gliomas
   E. Melanoma
   F. Germ Cell, Penile Cancer

G. Non-Small Cell Lung Carcinoma (NSCLC)
H. Other Advanced Solid Tumor Cancers/Malignancies

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Ripretinib (Qinlock) will be used as monotherapy (i.e., will not be used in combination with other oncologic medications); **AND**
IV. Member has experienced response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread

Supporting Evidence

I. Ripretinib (Qinlock) was evaluated in INVICTUS - a randomized (2:1), double-blind, placebo-controlled study in adults with advanced gastrointestinal stromal tumors. The trial included 129 subjects who had previously progressed on or after imatinib, sunitinib, and regorafenib, or had documented intolerance to any of these treatments despite dose modifications. Mutation status was collected but was not utilized as part of the inclusion criteria for this trial. Ripretinib (Qinlock) was evaluated as monotherapy, and use of ripretinib (Qinlock) in addition to other oncologic therapies has not been evaluated for safety and/or efficacy.
II. The primary efficacy endpoint was progression-free survival (PFS) and notable secondary endpoints included objective response rate (ORR), overall survival (OS), and quality of life (QOL). Ripretinib (Qinlock) showed statistically significant results in PFS compared to placebo [6.3 months vs. 1.0 months; HR 0.15; 95% CI 0.09-0.25; $p<0.001$]; however, there was not a statistically significant difference in ORR. Due to a hierarchal testing procedure of endpoints, overall survival and quality of life could not be formally tested for statistical significance given the insignificance of the ORR result.
III. The safety profile of ripretinib (Qinlock) is similar to that of other TKIs. The most common treatment-related treatment emergent adverse events (occurring in 20% or more of patients in the ripretinib group) during the INVICTUS trial included alopecia, myalgia, nausea, fatigue, palmar-plantar erythrodysesthesia (also known as hand-foot syndrome), and diarrhea. There are no contraindications to ripretinib (Qinlock); however, warnings and precautions include: palmar-plantar erythrodysesthesia syndrome, new primary cutaneous malignancies, hypertension, cardiac dysfunction, risk of impaired wound healing, and embryo-fetal toxicity. Ripretinib (Qinlock) was studied in adult patients age 18 and older and has not been evaluated for safety and/or efficacy in pediatric patients. FDA-approval has only been granted for adult patients.
IV. Gastrointestinal Stromal Tumor (GIST) is a rare subtype of soft tissue sarcoma, thus a definitive diagnosis from a specialty provider is warranted.

V. NCCN Guidelines recommend ripretinib (Qinlock) as fourth-line therapy for the treatment of unresectable or metastatic GIST for those who have progressed after imatinib (Gleevec), sunitinib (Sutent), and regorafenib (Stivarga) with a Category 2A recommendation.

Investigational or Not Medically Necessary Uses

I. Ripretinib (Qinlock) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Third-line or prior treatment for Gastrointestinal Stromal Tumor
   B. Advanced Systemic Mastocytosis or other hematologic malignancies
   C. Soft Tissue Sarcoma
   D. Malignant Gliomas
   E. Melanoma
   F. Germ Cell, Penile Cancer
   G. Non-Small Cell Lung Carcinoma (NSCLC)
   H. Other Advanced Solid Tumor Cancers/Malignancies

References

1. Qinlock [Prescribing Information]. Deciphera Pharmaceuticals, LLC: Waltham, MA. May 2020.
2. National Comprehensive Cancer Network. NCCN Guidelines: Soft Tissue Sarcoma . Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1464
3. American Society of Clinical Oncology Guidelines. Gastrointestinal Stromal Tumors. J Clin Oncol 36:136-143. [January 10, 2018]
4. Blay J, Serrano C, et al. Ripretinib in patients with advanced gastrointestinal stromal tumors: a double-blind, randomized, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2020; 21: 923-34.
5. Janku F, Abdul Razak AR, Chi P, Heinrich MC, von Mehren M, Jones RL, Ganjoo K, Trent J, Gelderblom H, Somaiah N, Hu S, Rosen O, Su Y, Ruiz-Soto R, Gordon M, George S. Switch Control Inhibition of KIT and PDGFRA in Patients With Advanced Gastrointestinal Stromal Tumor: A Phase I Study of Ripretinib. J Clin Oncol. 2020 Aug 17:JCO2000522. doi: 10.1200/JCO.20.00522. [Epub ahead of print]
6. Nemunaitis J, Bauer S, Blay JY, Choucair K, Gelderblom H, George S, Schöffski P, Mehren MV, Zalcberg J, Achour H, Ruiz-Soto R, Heinrich MC. Intrigue: Phase III study of ripretinib versus sunitinib in advanced gastrointestinal stromal tumor after imatinib. Future Oncol. 2020 Jan;16(1):4251-4264. doi: 10.2217/fon-2019-0633. Epub 2019 Nov 22.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP208

Description

Risdiplam (Evrysdi) is an orally administered survival of motor neuron 2 (SMN2) splicing modifier.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
risdiplam (Evrysdi)	Spinal Muscular Atrophy	60 mg/80 mL (0.75 mg/mL) solution	240 mL/30 days

Initial Evaluation

I. **Risdiplam (Evrysdi)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, a neuromuscular specialist; **AND**
   B. Provider attestation that nusinersen (Spinraza) will not be used concurrently with risdiplam (Evrysdi); **AND**
   C. A diagnosis of **5q spinal muscular atrophy (SMA)** when the following are met:
      1. Homozygous deletion of the *SMN1* gene or dysfunctional mutation of the *SMN1* gene; **AND**
      2. Provider attests member does not require invasive ventilation or tracheostomy; **AND**
      3. Provider attestation the member has not had treatment with onasemnogene abeparvovec-xioi (Zolgensma); **AND**
      4. Member must have ONE of the following SMA phenotypes:
         i. Pre-symptomatic SMA with two or three copies of the *SMN2* gene; **OR**
         ii. SMA Type I; **OR**
         iii. SMA II with symptomatic disease (e.g., impaired motor function and/or delayed motor milestones); **OR**
         iv. SMA III with symptomatic disease (e.g., impaired motor function and/or delayed motor milestones); **AND**
      5. Baseline documentation of at least ONE of the following motor function/milestone measures:
         i. Members less than two years of age:
            a. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), OR Hammersmith Infant Neurologic Exam (HINE); **OR**
         ii. Members two years of age or older:

a. Motor Function Measure 32 (MFM32), Revised Upper Limb Module (RULM), Hammersmith Functional Motor Scale Expanded (HFMSE), OR Six-Minute Walk Test (6MWT).

II. Risdiplam (Evrysdi) is considered investigational when used for all other conditions, including but not limited to:
   A. Use in members with Type IV SMA
   B. Use in combination with nusinersen (Spinraza)
   C. Use after treatment with onasemnogene abeparvovec-xioi (Zolgensma)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has responded to therapy, defined as stability or improvement in net motor function/milestones, compared to pretreatment baseline as exemplified by at least ONE of the following:
   A. Members less than two years of age:
      1. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), Hammersmith Infant Neurologic Exam (HINE), OR Bayley Scales of Infant Development–Third Edition (BSID-III) Item 22; **OR**
   B. Members two years of age or older:
      1. Motor Function Measure 32 (MFM32), Revised Upper Limb Module (RULM), Hammersmith Functional Motor Scale Expanded (HFMSE), OR Six-Minute Walk Test (6MWT); **OR**
   C. Provider attests that member has had a slowed rate of decline in the aforementioned measures compared to pretreatment rate.

Supporting Evidence

I. Spinal Muscular atrophy (SMA) is an autosomal recessive genetic disorder caused by mutations in chromosome 5q that lead to survival motor neuron (*SMN*) protein deficiencies. *SMN* protein from the *SMN1* gene, located on chromosome 5, is expressed in all cells and is required for life. In order to develop SMA, an individual must inherit two faulty *SMN1* genes, one from each parent; however, the majority of mutations responsible for 5q-SMA are either deletions or gene conversions.
II. SMA subtype/phenotype is determined primarily by motor milestone attained. Risdiplam (Evrysdi) is FDA approved to treat pediatric and adult patients with pre-symptomatic or symptomatic SMA. Pre-symptomatic patients do not present with symptoms of SMA but have been genetically diagnosed in utero or via newborn screening. SMA trials have shown that patients who begin treatment earlier may have more favorable outcomes.

III. Risdiplam (Evrysdi) is being evaluated in two ongoing Phase 2/3 trials (FIREFISH, SUNFISH) and an ongoing, phase 2 trial (RAINBOWFISH). FIREFISH is evaluating patients with infantile-onset Type I SMA and SUNFISH is evaluating patients with later-onset Type II and non-ambulatory Type III. RAINBOWFISH is enrolling pre-symptomatic infants two months of age or younger with SMA. All three studies require a confirmed diagnosis of 5q-autosomal recessive SMA prior to enrollment. Patients requiring invasive ventilation or tracheostomy are excluded from all three clinical trials (FIREFISH, SUNFISH, RAINBOWFISH); therefore, there are no data to show efficacy and safety in this patient population.

IV. FIREFISH is an open-label, two-part study designed to assess safety, tolerability, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD). The study included 21 patients in Part One and 41 patients in Part Two aged one to seven months with Type I SMA. The following endpoints were used: Bayley Scales of Infant Development–Third Edition (BSID-III) Item 22, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), and Hammersmith Infant Neurologic Exam (HINE).

- BSID-III is a clinical evaluation developed to help identify children with developmental delay who may require intervention services. The BSID-III consists of three areas of development: cognitive, language, and motor. Effectiveness was established based on the ability to sit without support for at least five seconds (as measured by Item 22). This scale is intended for pediatrics only and is not specific to SMA.
- CHOP-INTEND is a validated, 16-item, 64-point scale, designed to measure motor function for weak infants with Type I SMA and is intended for pediatrics only. It measures spontaneous upper and lower extremity movement, hand grip, head in midline with visual stimulation, hip adductors, rolling from legs and arms, shoulder and elbow flexion by itself and in addition to horizontal abduction, knee extension, hip flexion an foot dorsiflexion, head control, head/neck extension, and spinal incurvation. Each of the 16 items is graded on a scale of zero to four, with zero meaning no response and four meaning complete response.
- HINE-2 is an SMA-specific measurement, 8-item, 26-point scale, designed to measure motor skills in infants with SMA. A score of zero for items such as sitting, crawling, and walking is expected for Type I. It measures voluntary grasp, ability to kick, head control, rolling, sitting, crawling, standing, and walking.
- The primary efficacy outcome in FIREFISH Part One was dose determination for Part Two of the study, which was 0.2 mg/kg/day. The primary efficacy outcome in FIREFISH Part Two was the proportion of infants sitting without support for at least five seconds as assessed by the Gross Motor Scale of the BSID-III at Month 12, which was 29% (90% Cl: 17.8 to 43.1%). Key secondary efficacy outcomes in FIREFISH Part One include BSID-III at Month 12, which was 33%; infants alive with no permanent ventilation, 90.5%; proportion of infants who require hospitalization, and 38% did not require hospitalization. Key secondary efficacy outcomes in FIREFISH Part Two include HINE-2, which was 78% ($p<0.0001$) while the proportion of patients who achieved at least four points on the CHOP-INTEND score was 90% ($p<0.0001$).

V. SUNFISH is a two-part randomized, placebo-controlled study designed to assess safety, tolerability, efficacy, PK, and PD. The study included 51 patients in Part One and 180 patients in Part Two aged two to 25 with Type II or III SMA. Patients in Part Two of SUNFISH were randomized. The following endpoints were used: Motor Function Measure 32 (MFM-32) and Revised Upper Limb Module (RULM).

- MFM-32 is a 32-item scale that measures motor function abilities that relate to daily functions. The total MFM-32 score is expressed as a percentage (range: zero to 100) of the maximum possible score, with higher scores indicating greater motor function. This scale is suitable for assessing gross and fine motor skills in children and adult patients.
- RULM is a 19-item scorable scale used to assess motor performance of the upper limb in ambulatory and non-ambulatory patients with SMA. It tests proximal and distal motor functions of both upper limbs. The total score ranges from zero (all the items cannot be performed) to 37 (all the activities are achieved fully without any compensatory maneuvers). Each item is scored from zero to two: zero= unable, one=able with modification, two=able with no difficulty. RULM is applicable to both children and adults with SMA.
- The primary efficacy outcome in SUNFISH Part Two was the change from baseline to Month 12 in the MFM32 score in risdiplam (Evrysdi) vs. placebo, which was 1.36 (95% CI 0.61, 2.11) vs. -0.19 (-1.22, 0.84), with a difference from placebo of 1.55 (95% CI 0.30, 2.81, p=0.0156). Key secondary outcomes in SUNFISH Part Two include the proportion of patients with a 3-point or greater change from baseline to Month 12 in the MFM32 total score in risdiplam (Evrysdi) vs. placebo, which was 38.3% (28.9, 47.6) vs. 23.7% (12.0, 35.4), with a difference from placebo of 2.35 (1.01, 5.44), p-value=0.0469; change from baseline in total score of RULM at Month 12 in risdiplam (Evrysdi) vs. placebo of 1.61 (1.00, 2.22) vs. 0.02 (-0.83, 0.87), with a difference from placebo of 1.59 (0.55, 2.62), p-value=0.0469.

VI. While primary endpoint was measured at Month 12, patients showed improvement at Month 6. In FIREFISH Part Two, 38 of 41 infants surpassed responder threshold (≥4-point CHOP-INTEND improvement) at Month 6. Moreover, at Month 12, the same number of infants (38 of 41) achieved ≥4-point CHOP-INTEND improvement. SUNFISH Part Two had follow-up visits every five weeks and appeared to significantly show greater changes in MFM32 from baseline compared to placebo starting at week 16.

VII. RAINBOWFISH is an ongoing phase 2 open-label, single-arm study designed to assess efficacy and safety of risdiplam (Evrysdi) in infants less than two months of age with pre-symptomatic SMA. The primary endpoint will assess the efficacy of risdiplam (Evrysdi) in infants with two *SMN2* copies and CMAP ≥1.5 mV at baseline based on the ability to sit without support for at least 5 seconds as measured by Item 22 of the Gross Motor Scale of the BSID-III after 12 months on treatment. Secondary endpoints will evaluate all enrolled infants (regardless of *SMN2* copy number) on the development of clinical symptoms of SMA, achievement of motor milestones as defined in the BSID-III and the HINE-2, ability to swallow and feed orally, CHOP-INTEND motor function scale, growth measures, and time to permanent ventilation and/or death.

- A total of 26 patients with pre-symptomatic SMA are currently enrolled and preliminary data (data cut off July 2021) is available for 7 patients (four patients had 2 copies of the *SMN2*, two patients had 3 copies, and one patient had >4 copies) treated with risdiplam (Evrysdi) for at least 12 months. Interim efficacy data showed patients treated with risdiplam (Evrysdi) achieved motor milestones (measured by the HINE-2) within WHO windows for healthy children at 12 months. All seven patients were alive at 12 months without permanent ventilation, achieved sitting without support, were able to feed exclusively by mouth, and maintained the ability

to swallow solid food. In the six patients with two or three copies of the *SMN2* genes, four patients (67%) were able to stand and 3 patients (50%) were able to walk independently at month 12. Interim safety data is consistent with the safety profile of risdiplam (Evrysdi) for pediatric and adult patients with symptomatic SMA. The most common adverse events included teething (33%), nasal congestion (28%), and pyrexia (28%). There were no reported deaths or treatment-related adverse events that led to withdrawal at data cut off. No treatment related serious adverse events were reported in patients treated for up to 22.8 months. Full efficacy and safety data RAINBOWFISH has not been published.

VIII. Baseline documentation of motor function/milestones for patients younger than 2 months of age proactively requesting risdiplam (Evrysdi) may not be available at the time of the request. To avoid delaying access to initial therapy in recently diagnosed infants, assessments completed shortly posttherapy may serve as baseline.

IX. Other acceptable motor measurements not measured in risdiplam (Evrysdi) trials, but are validated are the following: Hammersmith Functional Motor Scale Expanded (HFMSE) and Six-Minute Walk Test (6MWT)

- HFMSE is a 33-item scorable scale used to assess motor function in people with SMA Type II or Type III; this is intended for individuals older than 24 months of age. Each item is scored from zero (lowest item grade) to two (highest item grade), with a maximum score of 66. Higher scores indicate increased levels of ability. Scorable items include, but not limited to, plinth/chair sitting, long sitting, one to two hands to head in sitting, spine to side-lying, rolls prone to supine over right and left, rolls supine to prone over right and left, sitting to lying, props on forearms, lifts head from prone, prop on extended arms, lying to sitting, 4-point kneeling, crawling, and stepping.
- 6MWT is an objective evaluation of functional exercise capability in ambulatory patients with later-onset (Type II or Type III) SMA. This test is based on distance where the patient walks as far as possible in six minutes; test is performed on a linear 25-meter marked course.

X. As of December 2022, the International Conference on the Standard of Care for Spinal Muscular Atrophy guidelines have not been updated to include risdiplam (Evrysdi) for the treatment of SMA.

XI. Per the Working Group for SMA-positive infants (comprised of 15 SMA experts), a pediatrician's expertise in child healthcare may be broad and not cover the unique features of a rare neuromuscular disorder; similarly, a general child neurologist may not specialize in the role of the neuromuscular system of the patient's symptomatology and diagnosis and may not have the knowledge to administer the specific tests being recommended here. A neuromuscular specialist would have the deepest knowledge of the clinical manifestations of SMA in order to detect the earliest symptomatology, in addition to experience with administering the highly sensitive assessments of motor neuron function and SMA specific motor function.

XII. Nusinersen (Spinraza) is a chronic, intrathecally administered therapy and onasemnogene abeparvovec-xioi (Zolgensma) is a one-dose treatment. Use of risdiplam (Evrysdi) in patients (1-60 years of age) previously treated with approved or investigational therapies for SMA is currently being studied in the JEWELFISH trial. Forty-four (n=77) of those enrolled had previously been treated with nusinersen (Spinraza), 8% (n=14) with onasemnogene abeparvovec

(Zolgensma), and the remaining 48% were previously treated with investigational therapies (RG7800* (n=13) and olesoxime* (n=71)). Out of the 14 patients previously treated with onasemnogene abeparvovec-xioi (Zolgensma), two enrolled in the trial due to lack of efficacy and eight enrolled to assess additional benefit after initial treatment. Interim exploratory efficacy data suggest stabilization in motor function measured by change from baseline in motor function measure (MFM-32) at 24 months of treatment and the overall adverse event profile of risdiplam (Evrysdi) has been consistent with that in treatment naïve patients; however data is limited. At this time, there is insufficient high-quality evidence to suggest the efficacy and safety of risdiplam (Evrysdi) in this patient population.

**RG7800 and olesoxime are no longer in development as investigational treatments for patients with SMA.*

Investigational Uses

I. Risdiplam (Evrysdi) has not been FDA approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Use in members with Type IV SMA
      i. Risdiplam (Evrysdi) has not be studied in this population.
   B. Use in combination with nusinersen (Spinraza)
      i. Risdiplam (Evrysdi) has not been studied to be used in combination use with nusinersen (Spinraza).
   C. Use after treatment with onasemnogene abeparvovec-xioi (Zolgensma)
      i. There is limited high quality evidence to suggest efficacy and safety of risdiplam (Evrysdi) in patients previously treated with onasemnogene abeparvovec-xioi (Zolgensma).

Appendix

I. There are no specific contraindications or warnings and precautions to using risdiplam (Evrysdi)
II. Table 1: risdiplam (Evrysdi) Adult and Pediatric Dosing Regimen by Age and Body Weight

Age and Body Weight	Recommended Daily Dosage
Less than 2 months of age	0.15mg/kg
2 months to less than 2 years of age	0.2 mg/kg
2 years of age and older weighing less than 20 kg	0.25 mg/kg
2 years of age and older weighing 20 kg or more	5 mg

References

1. Evrysdi [Prescribing Information]. Genentech, Inc: San Francisco, CA. May 2022.
2. Finkel R, Farrar M, Vlodavets D, et al. RAINBOWFISH: Preliminary efficacy and safety data in risdiplam treated infants with presymptomatic SMA. Presented at the Muscular Dystrophy Association Clinical and Scientific Conference in Virtual; March 13-16, 2022. MDA Clinical & Scientific Conference Poster.
3. Servais L, Al-Muhaizea M, Farrar MA, et al. RAINBOWFISH: A study of risdiplam in infants with presymptomatic spinal muscular atrophy (SMA). Presented at the World Muscle Society 2021 Virtual Congress September 20-24, 2021. WMS Oral Presentation.

4. Tizzano EF, Zafeiriou D. Prenatal aspects in spinal muscular atrophy: From early detection to early presymptomatic intervention. *Eur J Paediatr Neurol*. 2018;22(6):944-950. doi:10.1016/j.ejpn.2018.08.009
5. Mercuri E, Finkel RS, Muntoni F et al. Diagnosis and management of spinal muscular atrophy – Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscular Disorders 2018:103-115. Available from: https://www.nmd-journal.com/article/S0960-8966(17)31284-1/pdf
6. Finkel RS, Mercuri E, Meyer OH et al. Diagnosis and management of spinal muscular atrophy – Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscular Disorders 2018:197-207. Available from: https://www.nmd-journal.com/article/S0960-8966(17)31290-7/pdf
7. Glascock J, Samson J, Haidet-Phillips A et al. Treatment algorithm for infants diagnosed with spinal muscular atrophy through newborn screening. J Neuromuscular Diseases 2018:145-158. Available from: https://content-iospress-com.liboff.ohsu.edu/download/journal-of-neuromuscular-diseases/jnd180304?id=journal-of-neuromuscular-diseases%2Fjnd180304
8. SMA Care Series - The Genetics of Spinal Muscular Atrophy. Cure SMA. Retrieved September 21, 2020. Available from: https://www.curesma.org/wp-content/uploads/2020/09/09172020_Genetics-of-SMA_vWeb.pdf
9. Chiriboga CA, Bruno C, Duong T, et al. JEWELFISH: 24-month safety, pharmacodynamic and exploratory efficacy data in non-treatment-naïve patients with SMA receiving treatment with risdiplam. Presentation at: Annual Congress of the World Muscle Society; October 11-15, 2022. Halifax, Canada.

Related Policies

Currently there are no related policies.

Policy Implementation/Update

Action and Summary of Changes	Date
Updated supporting evidence and references regarding interim JEWELFISH study results.	12/2022
Modified criteria to limit coverage to patients not previously treated with onasemnogene abeparvovec-xioi to align with medical policies. Added prior treatment with onasemnogene abeparvovec-xioi to E/I. Updated supporting evidence.	09/2022
Updated criteria to include coverage in pre-symptomatic patients with two or three copies of SMN2 gene. Removed use in pre-symptomatic patients from E/I. Updated supporting evidence and references section.	06/2022
Policy created	11/2020

Policy Type: PA Pharmacy Coverage Policy: UMP105

Description

Roflumilast (Daliresp) is an oral phosphodiesterase 4 (PDE4) inhibitor that selectively inhibits a cyclic-AMP (cAMP) metabolism in the lung tissue.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
generic roflumilast	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	250 mcg tablet	Initial month: 30 tablets/30 days*
		500 mcg tablet	30 tablets/30 days
roflumilast (Daliresp)		250 mcg tablet	Initial month: 30 tablets/30 days*
		500 mcg tablet	30 tablets/30 days

**Coverage of 250 mcg daily dose limited to one month for medication titration; quantity exceptions not allowed.*

Initial Evaluation

I. **Roflumilast (Daliresp**) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Diagnosis of severe or very severe COPD (GOLD 3 or 4; FEV_1 < 50% predicted); **AND**
   C. Diagnosis of chronic bronchitis; **AND**
   D. Member has a history of at least one COPD exacerbation in the past year; **AND**
   E. Triple therapy with long-acting beta agonist (LABA), long-acting muscarinic antagonist (LAMA), and inhaled corticosteroid (ICS) has been ineffective, contraindicated, not tolerated or will be continued with roflumilast (Daliresp) [see appendix for examples]; **OR**
      1. Dual therapy with LABA and LAMA therapy has been ineffective, contraindicated, or not tolerated if eosinophil level is < 100 cells/uL; **AND**
   F. At least one long-acting bronchodilator therapy (LAMA and/or LABA) will be continued in combination with roflumilast (Daliresp); **AND**
   G. Request is for generic roflumilast (generic for Daliresp), unless member has a contraindication to generic product

II. Roflumilast (Daliresp) is considered <u>not medically necessary</u> when criteria above are not met and/or when used for:

A. Roflumilast (Daliresp) daily dose of 250 mcg for longer than the one-month initiation period for tolerability. This has been deemed a subtherapeutic dose by the drug manufacturer and FDA.

III. Roflumilast (Daliresp) is considered investigational when used for all other conditions, including but not limited to:
   A. Pediatric COPD
   B. Asthma

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Provider attestation of one of the following:
   A. The member has exhibited stability or improvement in rate or severity of exacerbations or improvement in lung function; **OR**
   B. Continuation of therapy is medically necessary despite lack of benefit in exacerbations or lung function (documentation is required).

Supporting Evidence

I. Roflumilast (Daliresp) starting dose is 250 mcg per day to improve tolerability and reduce likelihood of discontinuation due to adverse effects; however, this dose is subtherapeutic. The 250 mcg tablets are administered once daily for four weeks; thereafter, 500 mcg daily is used for maintenance. A 250mcg daily maintenance or quantity exceptions to utilize two x 250 mcg tablets daily are not covered. The 500mcg tablet is administered once daily and has an extended half-life, eliminating the need for twice daily dosing. Additionally, the 500mcg tablet is more cost efficient.

II. Roflumilast (Daliresp) is indicated to reduce the risk of COPD exacerbations in patients with severe or very severe COPD associated with chronic bronchitis and have a history of exacerbations. It has only been evaluated in adults; safety and efficacy are unknown when used in pediatrics. COPD does not normally occur in children and rare cases may be due to genetic conditions; however, roflumilast (Daliresp) has unknown consequences in these settings.

III. Chronic bronchitis is defined as chronic productive cough for three months in each of two successive years in a patient whom other causes of chronic cough have been excluded.

IV. Effects of roflumilast (Daliresp) have been evaluated in nine phase 3 clinical trials and other supplemental studies. The majority of trials failed to show clinical improvement in lung function, exacerbation rate, survival, or quality of life in the general COPD population. Exploratory analyses of early clinical trials identified a subpopulation of patients that appeared to demonstrate a better response to roflumilast (Daliresp); those with severe COPD associated with chronic bronchitis that have a history of COPD exacerbations within the last year. Several clinical trials have demonstrated lack of clinical benefit of roflumilast (Daliresp) in an unselected

patient population with COPD. Given the lack of benefit outside of the FDA-approved population coupled with specific safety concerns (e.g., psychiatric adverse effects including but not limited to suicide and suicidal ideation), coverage is limited to a narrow population.

V. The FDA-approval for roflumilast (Daliresp) is based on trials five and six of the clinical program that demonstrated a modest reduction in exacerbations vs. placebo and a statistically significant, but non-clinically significant, increase in FEV1. Patients were allowed to be on LABA or short-acting muscarinic antagonist (SAMA) therapy, and all patients had at least one recorded exacerbation requiring systemic corticosteroids or hospital admission within the previous year.

VI. A Cochrane Systematic Review of PDE4 inhibitors for COPD was conducted in 2020 to evaluate the extensive evidence for roflumilast (Daliresp) and other non FDA-approved therapies in this class. The conclusions of the review are as follows: PDE4 inhibitors in people with COPD may have additional but limited value and act independently of bronchodilators in patients with COPD. These therapies have a small benefit over placebo in reducing lung function or reducing likelihood of exacerbations. There is no known impact on quality of life or symptom control; however, there is cautious support for use and the identified place in therapy is as add-on therapy for patients with persistent symptoms or exacerbations despite optimal COPD management.

VII. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2022 report stance: roflumilast (Daliresp) may reduce exacerbation rates in those with severe or very severe COPD with chronic bronchitis and a history of exacerbations – mirroring the FDA approved indication. It is noted that roflumilast (Daliresp) benefits may be greater in patients with a prior hospitalization for acute COPD exacerbation; however, it is unknown if the benefit is selective to those with prior exacerbation requiring hospitalization (subgroup analyses of trials signal a greater benefit in those with prior hospitalization). The GOLD report recommends the following therapy in patients with persistent exacerbations despite long-acting bronchodilator monotherapy:

- Escalate to LABA/LAMA or LABA/ICS unless eosinophil level is < 100 cells/uL.
- In those with exacerbation while on LABA/ICS: add a LAMA or switch to LABA/LAMA.
- In those with exacerbation on either triple therapy LABA/LAMA/ICS or in those with exacerbation on dual therapy with LABA/LAMA for which ICS was inappropriate: roflumilast (Daliresp) may be added in the setting of severe or very severe disease, chronic bronchitis, and if patients have a history of exacerbation; particularly in those that have been hospitalized for an exacerbation in the previous year.

VIII. The Canadian Thoracic Society and European Respiratory Society/American Thoracic Society guidelines provide similar recommendations for use or roflumilast (Daliresp). Roflumilast (Daliresp) is not a bronchodilator therapy and should not be used for the relief of acute bronchospasm. It is not recommended to be used as monotherapy given lack of benefit in symptom control or quality of life, and the medication has unknown effects on exacerbation rate when used alone. It is recommended that dual or triple therapy be used prior to initiation of roflumilast (Daliresp) and that at least one bronchodilator (LABA and/or LAMA) be continued with roflumilast (Daliresp). It is also appropriate for roflumilast (Daliresp) to be added to triple therapy (LABA/LAMA/ICS). Some evidence suggests that roflumilast (Daliresp) may have additive effects with ICS; however, ICS may not be appropriate for all patients (e.g., not tolerated, low eosinophil level). When eosinophil levels are < 100 cells/uL, it is unlikely that ICS will be an

effective therapy for patients with COPD and is not a required therapy under this condition. When eosinophil level is adequate and tolerated, ICS is guideline recommended therapy prior to treatment initiation with roflumilast (Daliresp).

Investigational or Not Medically Necessary Uses

I. Roflumilast (Daliresp) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below and are considered experimental and investigational:
   A. Pediatric COPD
   B. Asthma

II. Roflumilast (Daliresp) daily dose of 250 mcg for longer than the one-month initiation period for tolerability is considered not medically necessary. This has been deemed a subtherapeutic dose by the drug manufacturer and FDA.

Appendix

I. GOLD Classification of Airflow Limitation Severity in COPD
   A. GOLD 1: Mild COPD, FEV1 is ≥ 80% predicted
   B. GOLD 2: Moderate COPD, FEV1 is ≥ 50% predicted but < 80% predicted
   C. GOLD 3: Severe COPD, FEV1 is ≥ 30% predicted but <50 predicted
   D. GOLD 4: Very Severe COPD, FEV1 is < 30% predicted

II. Long-acting beta agonists (LABA):
   A. Formoterol (Foradil Aeorolizer)
   B. Salmeterol (Serevent Diskus)
   C. Olodaterol (Striverdi Respimat)
   D. Formoterol (Performist)
   E. Arformoterol (Brovana)
   F. May also be a part of combination inhalers: budesonide/formoterol (Symbicort), fluticasone/umeclidinium/vilanterol (Trelegy Ellipta), budesonide/glycopyrrolate/formoterol (Breztri Aerosphere), fluticasone/salmeterol (Advair, AirDuo, generic), fluticasone/vilanterol (Breo Ellipta), etc.

III. Long-acting muscarinic antagonists (LAMA):
   A. Umeclidinium (Incruse Ellipta)
   B. Glycopyrrolate (Seebri Neohaler, Lonhala), aclidiium (Tudorza Pressair), tiotropium (Spiriva)
   C. May also be a part of combination inhalers: umeclidinium/vilanterol (Anoro), tiotropium/olodaterol (Stiolto), glycopyrrolate/formoterol (Vevespi), and glycopyrronium/indacaterol (Ultibron), etc.

IV. Inhaled corticosteroids (ICS)
   A. Mometasone (Asmanex)
   B. Beclomethasone (Qvar)
   C. Budesonide (Pulmicort)
   D. Fluticasone (Flovent, Armonair)
   E. May also be part of combination inhalers, see above, etc.

Related Policies

Currently there are no related policies.

References

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2022 Report. Global strategy for prevention, diagnosis and management of chronic obstructive disease. National Institutes of Health, National Heart, Lung, and Blood Institute; Available at http://www.goldcopd.com/. Accessed July 7, 2022.
2. Daliresp [Package Insert]. Wilmington, DE. AstraZeneca Pharmaceuticals LP. Revised March, 2022.
3. Shen LF, Lv XD, Chen WY, Yang Q, Fang ZX, Lu WF. Effect of roflumilast on chronic obstructive pulmonary disease: a systematic review and meta-analysis. Ir J Med Sci. 2018;187(3):731-738.
4. Naseem S, Hassan M, Akhtar SN, Syed F, Khan NU, Usman M. Effectiveness of roflumilast in treating chronic obstructive pulmonary disease: a systematic review and meta-analysis. Cureus. 2022;14(3):e22843.
5. Janjua S, Fortescue R, Poole P. Phosphodiesterase-4 inhibitors for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2020;5:CD002309.
6. Wedzicha JA, Calverley PMA, Albert RK, et al. Prevention of copd exacerbations: a european respiratory society/american thoracic society guideline. European Respiratory Journal. 2017;50(3).
7. Bourbeau J, Bhutani M, Hernandez P, et al. Canadian Thoracic Society Clinical Practice Guideline on pharmacotherapy in patients with COPD – 2019 update of evidence. Canadian Journal of Respiratory, Critical Care, and Sleep Medicine. 2019;3(4):210-232.

Policy Implementation/Update

Action and Summary of Changes	Date
Added requirement to try and fail generic roflumilast prior to using branded Daliresp	10/2022
Allowance of 250 mcg dose limited to one month titration period; Removal of requirement of recent hospitalization; Reworded to include very severe COPD patients for coverage allowance; Update to allow bypassing of ICS when eosinophil level is < 100 cells/uL; Updated to require continuation of a long-acting bronchodilator; Removal of requirement to continue ICS; Addition of adult age requirement. Policy updated to current format with inclusion of supplementary sections: E/I, NMN, Appendix, Related Policies. Added detailed supporting evidence.	08/2022
Criteria transitioned to policy format, with the following changes: further clarification around severe COPD definition, dose limit that it does not exceed 500 mcg per day if request is for a dose increase, supporting evidences were updated, and GOLD 2020 Report was updated.	11/2019
Criteria created	04/2018

Policy Type: PA/SP Pharmacy Coverage Policy: UMP257

Split Fill Management*

Description

Ropeginterferon alfa-2b-njft (RIFN-α-2b; Besremi) is a long-acting, monopegylated, interferon alfa isomer which induces cellular activities related to binding specific cell-surface membrane receptors.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
ropeginterferon alfa-2b-njft (Besremi)	500 µg/mL pre-filled syringe (PFS)	Polycythemia Vera (PV)	2 syringes/28 days

Initial Evaluation

I. **Ropeginterferon alfa-2b-njft (Besremi)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with an oncologist or hematologist; **AND**
   C. A diagnosis of **polycythemia vera (PV)** when the following are met:
      1. Provider attests that the member has high-risk PV and requires cytoreductive therapy; **AND**
      2. Treatment with both of the following has been ineffective or not tolerated, unless all are contraindicated:
         i. Hydroxyurea
         ii. Peginterferon alfa-2a (Pegasys); **AND**
      3. Ropeginterferon alfa-2b-njft (Besremi) is medically necessary for the treatment of polycythemia vera (PV) over hydroxyurea and peginterferon alfa-2a (Pegasys). (Note: preference for longer injection interval or other convenience does not meet medical necessity).

II. Ropeginterferon alfa-2b-njft (Besremi) is considered investigational when used for all other conditions, including but not limited to:
   A. Myelofibrosis

B. Essential thrombocythemia
C. Chronic hepatitis infection (e.g., hepatitis B, hepatitis C)
D. Acute myeloid leukemia (AML)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited disease improvement or stability (e.g., complete hematological response (CHR), improved hematocrit ≤ 45%, platelet and WBC counts within normal range).

Supporting Evidence

I. RIFN-α-2b (Besremi) is FDA-approved for the treatment of adult patients with PV. PV is a rare, chronic, myeloproliferative disorder caused by a mutation in bone marrow stem cells resulting in blood cell overproduction. Symptoms include pruritis, fatigue, and microcirculatory disturbance. PV may progress to myelofibrosis and acute myeloid leukemia (AML).
II. PV risk stratification is based on age and comorbidities. Patients ≥ 60 years at initial diagnosis and presence of cardiovascular comorbidities or thromboembolic event history are classified as high-risk. Risk level guides treatment. For low-risk PV, periodic phlebotomy combined with low-dose aspirin remain the first-line therapy. Patients with high-risk PV may require cytoreductive therapy. Additionally, low-risk PV patients, who are symptomatic after repeated phlebotomy may be considered as potential candidates for cytoreductive therapy. This may consist of patients who experience new thrombosis, splenomegaly, progressive thrombocytosis, or disease-related major bleeding event when being managed via phlebotomy. These patients, even though classified as low-risk PV cases, are recommended to be treated similar to high-risk PV. Cytoreductive therapy may be considered medically necessary in this subgroup of patients.
III. The National Comprehensive Cancer Network (NCCN) guideline for the treatment of myeloproliferative neoplasms recommend hydroxyurea (HU) or peginterferon alfa-2a (Pegasys) as preferred cytoreductive agents. In practice, peginterferon alfa-2a (Pegasys) may be considered for younger patients, during pregnancy or where treatment with HU is contraindicated. For patients with intolerance or resistance to other cytoreductive agents, ruxolitinib (Jakafi) is a recommended subsequent-line therapy. As of March 2022, the NCCN guideline added RIFN-α-2b (Besremi) as 'other recommended regimen' (Category 2A) for the treatment of high-risk PV. Additionally, RIFN-α-2b (Besremi) may also be considered as another recommended regimen, when used adjunct to phlebotomy, for the initial treatment of low-risk PV. This recommendation is based on lower-level evidence (Category 2B). Current clinical data for RIFN-α-2b (Besremi) does not provide a high degree of confidence for use in the initial treatment of patients with low-risk PV, and cytoreductive treatment naïve patients.
IV. FDA-approval is based on efficacy data from a single-arm, open-label Phase 1/2 clinical trial (PEGINVERA) and safety profile assessed via subsequent open-label, randomized, active-controlled Phase 3 trials (PROUD-PV, CONTINUATION-PV) in addition to PEGINVERA.

- Phase 1/2 study: patients (N=51) were newly diagnosed, had exposure to HU, any risk level disease, and refractory to phlebotomy. RIFN α-2b (Besremi) led to an overall hematological response of 75% at week 10, with 26% reported as complete response (CR). Additionally, 74% patients achieved a Hct ≤ 45% at 12 months.
- Phase 3 trials: Two concurrent randomized Phase3I trials assessed RIFN-α-2b (Besremi) versus standard therapy (HU): PROUD-PV to assess non-inferiority of RIFN-α-2b (Besremi) to HU over 12 month regimen; CONTINUATION-PV: to assess CHR and improvement in disease burden at 36 months of therapy. Primary endpoint results for these trials were not statistically significant and non-inferiority to HU was not shown. However, RIFN-α-2b (Besremi) improved long-term disease response and CHR at 36 months vs. HU.

V. Prescribing information for RIFN-α-2b (Besremi) includes a black box warning for fatal or life-threatening neuropsychiatric, autoimmune, ischemic and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations.

VI. For those with high-risk PV and require cytoreductive therapy, HU is the preferred first-line therapy given the extensive history of use, established safety profile, efficacy and cost-effectiveness. Although not FDA-approved for the treatment of PV, peginterferon alfa-2a (Pegasys) has found its place as an alternative cytoreductive agent, with supportive data from multiple clinical trials and retrospective studies. Notably, a Phase 2 open-label clinical trial assessed Pegasys for induction of CR and PR in patients with high-risk PV (n=50), where in overall response rate of 60% (22% CR) was reported. Additional Phase 3 clinical trial (N=168) also assessed efficacy of Pegasys vs. hydroxyurea and reported comparable response rates.

VII. Currently available clinical data does not conclusively establish superiority of RIFN-α-2b (Besremi) over HU. Although RIFN-α-2b (Besremi) is purported to provide better acute tolerability due to longer interval between injections (14 days) versus Pegasys (7 days), efficacy and safety of RIFN-α-2b (Besremi) has not been compared with peginterferon alfa-2a (Pegasys) in a head-to-head clinical trial. At this time, real-world safety profile and patient experience with RIFN-α-2b (Besremi) remain largely unknown. Thus, preference toward bi-weekly dosing or convenience of administration does not establish medical necessity of RIFN-α-2b (Besremi) over peginterferon alfa-2a (Pegasys). Weighing the safety, efficacy, cost, and clinical experience, HU and peginterferon alfa-2a (Pegasys) are considered standard and appropriate high-value cytoreductive treatment options for the treatment of PV.

Investigational or Not Medically Necessary Uses

I. RIFN-α-2b (Besremi) has not been FDA-approved, or sufficiently studied for the treatment of any other condition, including other myeloproliferative neoplasms (e.g., essential thrombocythemia, myelofibrosis, acute myeloid leukemia (AML)).

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Gisslinger H, Zagrijtschuk O et al. Ropeginterferon alfa-2b, a novel IFNα-2b, induces high response rates with low toxicity in patients with polycythemia vera. Blood. 2015 Oct 8;126(15):1762-9.
2. Gisslinger H, Klade C et al. PROUD-PV Study Group. Ropeginterferon alfa-2b versus standard therapy for polycythaemia vera (PROUD-PV and CONTINUATION-PV): a randomised, non-inferiority, phase 3 trial and its extension study. Lancet Haematol. 2020 Mar;7(3):e196-e208.
3. NCCN clinical practice guideline in oncology: myeloproliferative neoplasms; V2.2021; updated 08/18/2021.
4. Ropeginterferon alfa-2b-njft (Besremi). Prescribing Information. 11/ 2021. PharmaEssentia USA Corp., Burlington MA.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
peginterferon alfa-2a (Pegasys)	Polycythemia vera
	Essential thrombocythemia
	Chronic hepatitis B
	Chronic hepatitis D

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2022

Policy Type: PA/SP Pharmacy Coverage Policy: UMP152

Split Fill Management*

Description

Rucaparib (Rubraca) is an orally administered poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the maintenance therapy, of ovarian, fallopian tube, or primary peritoneal cancer.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
rucaparib (Rubraca)	200 mg tablets	Maintenance for: recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer;	120 tablets/30 days
	250 mg tablets		
	300 mg tablets		

Initial Evaluation

I. **Rucaparib (Rubraca)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. Rucaparib (Rubraca) will be used as monotherapy; **AND**
   D. Member has not progressed on a prior PARP inhibitor (e.g., olaparib [Lynparza], niraparib [Zejula]) therapy; **AND**
   E. A diagnosis of one of the following:
      1. **Recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer**; **AND**
         i. Provider is requesting for maintenance therapy; **AND**
         ii. Member has experienced disease progression on or after at least TWO or more prior platinum-based chemotherapy regimens (e.g., cisplatin, carboplatin, oxaliplatin); **AND**
         iii. Member is in complete or partial response to their last platinum-based chemotherapy regimen (i.e., platinum sensitive); **AND**
         iv. Rucaparib (Rubraca) will be started within eight weeks of completion of the most recent platinum-based chemotherapy regimen; **OR**
         v. Provider attests with supporting documentation that member's recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer has not progressed since the most recent platinum-based chemotherapy regimen

II. Rucaparib (Rubraca) is considered investigational when used for all other conditions, including but not limited to:
   A. Used in combination with other chemotherapy or targeted therapy regimen
   B. Breast Cancer
   C. Prostate Cancer
   D. Advance Solid Tumors
   E. Melanoma
   F. Pancreatic cancer
   G. Gastroesophageal cancer
   H. Treatment of advanced ovarian cancer after 3 of more lines of therapy

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Rucaparib (Rubraca) will be used as monotherapy; **AND**
IV. Member has exhibited improvement or stability of disease symptoms (e.g., decrease in tumor size, or tumor spread).

Supporting Evidence

I. The safety and efficacy of rucaparib (Rubraca) in the setting of maintenance therapy for recurrent ovarian cancer was studied in a double-blind, multicenter trial (ARIEL3) where 564 adult patients with platinum-sensitive recurrent epithelial ovarian fallopian tube or primary peritoneal cancer. The patients were randomized 2:1 rucaparib (Rubraca) 600 mg orally daily or matched placebo within 8 weeks of their last dose of platinum-based therapy. The major efficacy outcome was progression-free survival (PFS) assessed by investigator, which ARIEL 3 demonstrated a statistically significant improvement in PFS in the rucaparib (Rubraca) arm as compared to the placebo arm. In the rucaparib (Rubraca) arm, the median PFS was 10.8 months compared to 5.4 months in the placebo arm with a hazard ratio (HR) of 0.36 and 95% CI (0.3, 0.45).
II. Therapy in the maintenance setting was initiated within eight weeks after completion of the last dose of platinum-based chemotherapy. The intent is that treatment is started within a reasonable timeframe consistent with a maintenance treatment plan (i.e., as close to 8 weeks as possible), but recognize that scheduling or other factors may impact the ability of a patient to start exactly within these first eight weeks.
III. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy to support the use of a subsequent PARP inhibitor following progression of disease on another PARP inhibitor.

Investigational or Not Medically Necessary Uses

I. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for the use of rucaparib (Rubraca) in the following settings listed below:
   A. Used in combination with other chemotherapy or targeted therapy regimen.
   B. Breast Cancer
   C. Solid Tumors
   D. Prostate Cancer
      1. Efficacy of rucaparib (Rubraca) was investigated in an ongoing multi-center, single arm clinical trial (TRITON2) in patients with *BRCA*-mutated metastatic castration-resistant prostate cancer (mCRPC), who had been treated with androgen receptor-directed therapy and taxane-based chemotherapy. There were 115 patients with either germline or somatic *BRCA* mutations enrolled in TRITON2, of whom 62 patients had measurable disease at baseline. Patients received rucaparib (Rubraca) 600 mg orally twice daily along with concomitant GnRH analog or had prior bilateral orchiectomy. Objective response rate (ORR) and duration of response (DOR) were assessed in patients with measurable disease by blinded IRR and by the investigator protocol. An ORR of 43.5% (n= 27; 31.0-56.7) was reported for IRR evaluation of 62 patients with measurable disease, while DoR was not estimable given the lack of data maturity. Quality of clinical evidence is low due to open label, single-arm trial design and lack of measurable survival outcomes and patient quality of life related outcomes. Of note, as of October 2020, rucaparib (Rubraca) is being studied in a phase 3 trial for mCRPC with other therapeutic agent(s) as active comparator (TRITON3) and results for this study are not available. Of note, another PARP-inhibitor, olaparib (Lynparza) is FDA-approved for treatment of mCRPC in patients who progressed on previous chemotherapy. Olaparib (Lynparza) was approved for this indication based on an open label phase 3 trial, which reported survival outcomes (rPFS and OS) and has a category 1 recommendation per NCCN guidelines for treatment of prostate cancer.
   E. Treatment of advanced ovarian cancer after 3 of more lines of therapy
      1. The safety and efficacy of rucaparib (Rubraca) for the treatment of advanced ovarian cancer after two or more chemotherapies was studied in two multicenter, single-arm, and open-label trials with 106 adult patients that have advanced BRCA-mutant ovarian cancer who had progressed after two or more prior chemotherapies. The efficacy outcomes were objective response rate (ORR) and duration of response (DOR) assessed by the investigator and independent radiology review; the average ORR was 54% and the average DOR was 9.2 months.
      2. In June 2022, the manufacturer of rucaparib (Rubraca) voluntarily withdrew the indication for treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens. This withdrawal was based on a totality of information from PARP inhibitors in the late line treatment setting in ovarian cancer. Specifically, following data from the Ariel4 postmarketing trial linking rucaparib (Rubraca) to an increased risk of death over chemotherapy in patients with third-line or later ovarian cancer despite the drug showing a benefit in stalling disease progression. Similar detrimental effects on overall

survival were observed with another PARP inhibitor in a randomized, active-controlled clinical trial conducted in a BRCA mutant 3L+ advanced ovarian cancer population.

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References

1. Rubraca [Prescribing Information]. Boulder, CO: Clovis Oncology, Inc. June 2022.
2. Coleman RL, Oza AM, Lorusso D, et al. Rucaparib Maintenance Treatment for Recurrent Ovarian Carcinoma After Response to Platinum Therapy (ARIEL3): A Randomized, Double-blind, Placebo-controlled, Phase 3 Trial. *Lancet.* 2017 Oct 390(10106): 1949–1961.
3. Abida W, Patnaik A, Campbell D, et al. Rucaparib in Men with Metastatic Castration-Resistant Prostate Cancer Harboring a *BRCA1* or *BRCA2* Gene Alteration. J Clin Oncol. 2020 Aug 14: JCO2001035. doi: 10.1200/JCO.20.01035.

Policy Implementation/Update:

Action and Summary of Changes	Date
Removal of ovarian cancer indication in the late line (3+) treatment setting following voluntarily withdraw of the indication by the manufacturer.	09/2022
Added split fill restriction given dose interruption/dose reduction rates. Corrected published QL to reflect 120/30. Confirmation of monotherapy use upon renewal.	08/2021
Updated supporting evidence for investigational use of rucaparib (Rubraca) for treatment of prostate cancer	11/2020
Criteria transition into policy with the following updates made: addition of supporting evidence and investigation section, broke out the different indications (treatment versus maintenance therapy), included mutation status for the treatment of recurrent ovarian cancer, included criterion around prior PARP inhibitor use, increase initial approval duration from three months to six months to be consistent with other payers, included age criterion per label, and removed the 8 weeks criterion around most recent platinum-based therapy in the setting of maintenance therapy in recurrent ovarian cancer; in place of the 8 weeks criterion, provider attestation and documentation is required instead.	12/2019

Policy Type: PA (Jakafi SP) Pharmacy Coverage Policy: UMP057

Split Fill Management* (applies to oral ruxolitinib [Jakafi] only)

Description

Ruxolitinib is a Janus Associated Kinase (JAK) inhibitor of JAK1 and JAK2. Ruxolitinib (Jakafi) is orally administered, and ruxolitinib (Opzelura) is a topical cream.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indications	Quantity Limit
ruxolitinib (Jakafi)	5 mg tablets	Intermediate or high-risk myelofibrosis Polycythemia vera	60 tablets/30 days *Quantity exceptions are not allowed. *The maximum number of ruxolitinib (Jakafi) tablets allowed is 60 tablets/30 days total if a combination of strengths is used
	10 mg tablets		
	15 mg tablets		
	20 mg tablets		
	25 mg tablets		
	5 mg tablets	Acute Graft-Versus-Host Disease Chronic Graft-Versus-Host disease	
	10 mg tablets		
ruxolitinib (Opzelura)	1.5 % cream	Atopic dermatitis	2 tubes/28 days (120 grams)
		Nonsegmental Vitiligo	

**Dose optimization will be required if the prescribed dose is unable to be reached at a quantity of 60/30. Use of two strengths may be necessary to reach target dose. Quantity is subject to 30/30 if multiple tablet strengths are utilized, for a maximum total allowed quantity of 60 ruxolitinib (Jakafi) tablets per 30-day supply.*

Initial Evaluation

I. **Ruxolitinib (Jakafi)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, an oncologist, hematologist, dermatologist, or immunologist; **AND**
   B. A diagnosis of one of the following:

1. **Intermediate-to-high-risk myelofibrosis (MF)** which includes primary MF, post-polycythemia vera MF, or post essential thrombocythemia MF; **OR**
2. **Polycythemia vera**; **AND**
    i. Treatment with hydroxyurea has been ineffective, contraindicated, or not tolerated; **OR**
3. **Graft versus-host disease (GVHD), acute or chronic; AND**
    i. Member is 12 years of age or older; **AND**
    ii. Documentation of moderate-to-severe GVHD (e.g., Grade 2 to 4 GVHD, OR Grade B to D); **AND**
    iii. The member has had an inadequate response to steroids (e.g., prednisone, methylprednisolone, beclomethasone, budesonide).

II. **Ruxolitinib (Opzelura)** may be considered medically necessary when the following criteria are met:
A. Member is 12 years of age or older; **AND**
B. A diagnosis of one of the following:
1. **Atopic Dermatitis**; **AND**
    i. Treatment with at least one agent in **ALL** of the following groups have been ineffective, contraindicated, or not tolerated:
        a. Group 1: topical corticosteroids (e.g., hydrocortisone, desonide, triamcinolone, betamethasone, clobetasol)
        b. Group 2: topical calcineurin inhibitors: tacrolimus (e.g., Protopic), pimecrolimus (e.g., Elidel)
        c. Group 3: topical phosphodiesterase 4 inhibitor: crisaborole (Eucrisa); **AND**
    ii. Provider attestation that the member will NOT use topical ruxolitinib (Opzelura) in combination with systemic JAK inhibitors (e.g., baricitinib [Olumiant], upadacitinib [Rinvoq], abrocitinib); **OR**
2. **Nonsegmental Vitiligo**; **AND**
    i. Chronic disease (greater than 6 months); **AND**
        a. A total body surface area that does **not** exceed 10%; **OR**
        b. Involves areas of the face, ears, or genitalia; **AND**
    ii. Treatment with at least one therapy in **EACH** the following categories has been ineffective or not tolerated, or are contraindicated:
        a. Phototherapy (UVB or PUVA); **AND**
        b. Topical calcineurin inhibitors: tacrolimus (e.g., Protopic), pimecrolimus (e.g., Elidel); **AND**
        c. Topical corticosteroids of at least high potency (e.g., betamethasone, mometasone, clobetasol, fluocinonide).; **AND**
    iii. Provider attestation that the member will NOT use topical ruxolitinib (Opzelura) in combination with other biologics, systemic JAK inhibitors (e.g., baricitinib [Olumiant], upadacitinib [Rinvoq], abrocitinib), or potent immunosuppressants (e.g., azathioprine, cyclosporine).

III. Ruxolitinib (Jakafi, Opzelura) is considered investigational when used for all other conditions, including but not limited to:
   A. Low risk myelofibrosis
   B. Acute leukemia
   C. COVID-19
   D. Alopecia areata
   E. Other vitiligo diseases outside of nonsegmental or other depigmentation disease
   F. Glioma and glioblastoma
   G. Hidradenitis suppurativa
   H. Malignancy or cancer outside of myelofibrosis

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. For **intermediate- to high-risk myelofibrosis (MF) OR polycythemia vera:**
   A. Request is for ruxolitinib (Jakafi); **AND**
      1. Documentation of reduction in spleen volume; **OR**
      2. Provider attestation of positive treatment response (e.g., improvement in symptoms, hematocrit control); **OR**
IV. For **graft versus-host disease (GVHD), acute or chronic:**
   A. Request if for ruxolitinib (Jakafi); **AND**
      1. Provider attestation of positive treatment response (e.g. reduction in symptoms associated with GVHD: gastrointestinal, ophthalmic, cutaneous, pulmonary); **OR**
V. For **atopic dermatitis:**
   A. Request is for ruxolitinib (Opzelura) topical treatment:
      1. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in IGA score from baseline, reduction in BSA involvement, pruritis symptom reduction); **AND**
      2. Provider attestation that the member will NOT use topical ruxolitinib (Opzelura) in combination with systemic JAK inhibitors (e.g., baricitinib [Olumiant], upadacitinib [Rinvoq], abrocitinib).
VI. For **nonsegmental vitiligo:**
   A. Request is for ruxolitinib (Opzelura) topical treatment:
      i. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in F-VASI and/or T-VASI score from baseline, reduction in BSA involvement, depigmentation reduction); **AND**
      ii. Provider attestation that the member will NOT use topical ruxolitinib (Opzelura) in combination with other biologics, systemic JAK inhibitors (e.g., baricitinib [Olumiant], upadacitinib [Rinvoq], abrocitinib), or potent immunosuppressants (e.g., azathioprine, cyclosporine).

Supporting Evidence

I. Length of authorization for initial approval is six months due to the clinical trial design, efficacy was evaluated at 24 weeks or less for all indications. Additionally, therapy beyond six months of treatment should be reserved for those where benefits outweigh the risks. For ruxolitinib (Jakafi) If no treatment response is seen at six months, therapy should be tapered into discontinuation. Therapy should not be abruptly discontinued given the potential for symptom proliferation and exacerbation.

II. The FDA-approved conditions for this therapy require specialized and individualized care and monitoring; thus, a specialist prescriber, or consultation with a specialist, is required.

III. Treatment for MF is based on risk. For intermediate-to high risk MF, stem cell transplant is the recommended treatment option; however, for those ineligible for stem cell transplant, hydroxyurea, fedratinib (Inrebic), and ruxolitinib (Jakafi) are available treatment options. While hydroxyurea may relieve splenomegaly and some symptoms of the condition (e.g., thrombocytosis, leukocytosis), it is thought to be less efficacious than other treatment options and may not be beneficial for major symptoms of the condition.

IV. Polycythemia vera treatment selection is also based on risk. Phlebotomy and/or low-dose aspirin are used in the management of low-risk disease. For high-risk disease, hydroxyurea is the preferred therapy given the extensive history of use, well-established safety profile, efficacy, and cost-effectiveness. Although busulfan has been used historically as a second-line therapy, because it has been associated with safety concerns such as cytopenia, pulmonary fibrosis, leukemia, and others, hydroxyurea remains the mainstay therapy. Ruxolitinib (Jakafi) is reserved for those that are not candidates for, or are refractory to, hydroxyurea, given the limited long-term safety and efficacy data. Additionally, for the treatment of polycythemia vera, ruxolitinib (Jakafi) is specifically FDA-approved after inadequate response or intolerance to hydroxyurea.

V. The FDA approval of ruxolitinib (Jakafi) in the setting of intermediate-to high-risk myelofibrosis was based on the results of two randomized Phase 3 trials. In Study 1, the primary endpoint was the proportion of participants achieving greater than, or equal to, a 35% reduction from baseline in spleen volume at Week 24. Secondary outcomes included proportion of patients achieving a 50% or greater reduction in Total Symptom Score from baseline to week 24. This was measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF), which incorporates abdominal discomfort, pain, night sweating, itching, bone and muscle pain, and early satiety. The study met statistical significance in all outcomes. In Study 2, the primary endpoint was the proportion of participants achieving greater than, or equal to, a 35% reduction from baseline in spleen volume at Week 48. This outcome was statistically significant.

VI. The FDA approval of ruxolitinib (Jakafi) in the setting of polycythemia vera was based on the result of a randomized, open-label, active-controlled Phase 3 study. The primary endpoint was the proportion of participants at Week 32 achieving hematocrit control in the absence of phlebotomy and spleen volume reduction. In the ruxolitinib (Jakafi) arm, 60% of the participants met the primary endpoint compared to 19% in the placebo arm. Participants must have had a resistance or intolerance to hydroxyurea.

VII. Graft-versus-host disease is a complication of allogenic hematopoietic cell transplant. Treatment is dependent on severity and location of disease. The GVHD Grade depends on severity and location, and ranges from I-IV. Grade I is reflective of skin involvement, Grade IV is severe disease with severe skin involvement (e.g., blistering) and internal organ involvement, and

Grade II-IV correlate with moderate to severe disease. The International Bone Marrow Transplant Registry Severity Index uses Grade A-D, which align with grading I-IV.

VIII. For Grade I or A, or mild disease, topical therapy is indicated. For Grade II or B or greater, or moderate-to-severe disease, systemic therapy is warranted. Glucocorticoids are the mainstay therapy; however, for those with glucocorticoid resistant disease, participation in clinical trials is recommended as there is currently no consensus on standard of care. Otherwise, therapies such as ruxolitinib (Jakafi) or ibrutinib (Imbruvica) are recommended. Therapy such as mycophenolate, rituximab, etanercept (Enbrel), everolimus, and others have been used historically, but there is lack safety and efficacy data from clinical trials to support the use of these therapies.

IX. The FDA approval of ruxolitinib (Jakafi) in the setting of acute GVHD was based on the results of an open-label, single-arm, multicenter study in participants with steroid-refractory acute GVHD Grades II to IV that were 12 years of age or older. Therapy was evaluated up to 10 mg twice daily. The efficacy of ruxolitinib (Jakafi) was based on a Day-28 overall response rate (ORR) by the Center for International Blood and Marrow Transplant Research (CIBMTR) criteria and the duration of response. The ORR was 57.1% with a median duration response of 16 days.

X. For chronic GVHD, ruxolitinib (Jakafi) was evaluated in a Phase 3, open-label, randomized trial against best available treatment (BAT). Patients were 12 years of age or older, steroid-refractory, and had moderate-to-severe disease. Outcomes were ORR, failure-free survival (FFS), and Lee Symptom Score. Ruxolitinib (Jakafi) was superior to BAT in all outcomes. Given the availability of objective and subjective positive outcomes in this condition, and lack of standard of care beyond glucocorticoids, there is moderate confidence that ruxolitinib (Jakafi) provides clinical value for this condition.

XI. To date, ruxolitinib (Jakafi) has not been shown to improve survival for any condition.

XII. The safety and efficacy of ruxolitinib (Jakafi), or any other JAK inhibitor has not been evaluated in patients under 12 years of age.

XIII. Split fill applies to ruxolitinib (Jakafi) given the high rates of treatment discontinuation due to adverse events, and the rates of dose reduction or interruption seen in clinical trials (e.g., in the pivotal trial for aGVHD the rate of treatment discontinuation due to adverse events was 31%).

XIV. Topical ruxolitinib is the first non-oral JAK inhibitor for the treatment of atopic dermatitis (AD). Emerging data are showing JAK inhibitors to be effective therapies; however, competing JAK therapies are oral systemic treatments: abrocitinib, upadacitinib (Rinvoq), and baricitinib (Olumiant).

XV. Nonpharmacologic treatment options for mild-to-moderate AD include emollients, wet wrap therapy, and phototherapy. Topical pharmacologic treatment options include corticosteroids (TCS), calcineurin inhibitors (TCI) (e.g., tacrolimus, pimecrolimus), and phosphodiesterase-4 inhibitor crisaborole (Eucrisa). Choice of therapy is dependent on severity, location, and other patient factors (e.g., allergies, age).

XVI. Ruxolitinib (Opzelura) was evaluated in two Phase 3, randomized, double-blind, vehicle-controlled studies in 872 adolescents and adults (TRuE-AD1 and TRuE-AD2) age 12 and older. Treatment arms: vehicle, ruxolitinib 0.75% or 1.5%. Treatment was used continuously for eight weeks, then patients from the vehicle arm were re-randomized 1:1 to ruxolitinib 0.75% or ruxolitinib 1.5% for an additional 44 weeks. Trial population characteristics included: At least 12 years of age, 60% were female, 70% were white, had a mean affected BSA of 9-10%, baseline

EASI of 8, 75% of patients had an IGA of 3, a mean NRS score of 5, median duration of AD of 16 years, and 40% of patients had facial involvement.

XVII. The primary outcome was proportion of patients achieving IGA treatment success (IGA-TS) (i.e., IGA score of 0 or 1 with at ≥ 2 grade improvement). Secondary outcomes were EASI75, change in EASI, and proportion of patients achieving ≥ 4-point improvement in the NRS itch score. At eight weeks, both ruxolitinib arms showed statistical and clinical superiority to vehicle in all outcomes. The 52-week assessments showed similar, or favorable outcomes.

XVIII. At eight weeks, rates of adverse events (AE) were similar among all treatment arms and were mild or moderate in severity. Common AE were burning (≤ 6.5%) and pruritis (3.2%). Discontinuation rates due to AE were ≤ 4%. Safety data out to 52 weeks did not reveal additional safety warnings. No serious AE occurred as a result of ruxolitinib (Opzelura) treatment; however, there was a relatively small patient population evaluated, and with data only out to 52 weeks there may be unrealized safety characteristics. Although two clinical trials showed consistent improvement in the outcomes noted above, there remains uncertainty in the following: place in therapy, safety and efficacy data when used in combination with other topical therapies and/or systemic treatments for AD, long term safety, durability of efficacy, and comparative efficacy to other topical agents. The safety and efficacy profiles of other topical therapies are well established, and data are lacking to show superior safety and efficacy of ruxolitinib (Opzelura) over these agents. Furthermore, there is lack of safety and efficacy data in pediatric patients under 12 years of age. Other topical therapies have been approved in this age group, and ruxolitinib is being evaluated in this population.

XIX. The safety profile of systemic JAKs is continuing to develop; however, the FDA has issued cardiovascular and malignancy warnings. The true safety profile of ruxolitinib (Opzelura) is unknown at this time, given the short trial duration and relatively small trial population. Utilizing a systemic JAK therapy in addition to topical JAK therapy has unknown, and potentially additive, risks. Until further data are available to establish a safety profile with this combination, dual use will be disallowed. For those in need of systemic and topical therapy, provider and patients should consider therapies and combination with alternative mechanisms, including, but not limited to, dupilumab, tralokinumab systemic therapies, and the aforementioned topical therapies.

XX. Ruxolitinib (Opzelura) 1.5% topical cream is FDA-approved at a maximum of 60 grams per week, and medication should not be applied to greater than 20% of the body surface area. Additionally, therapy should be used for short term and non-continuous treatment of mild to moderate atopic dermatitis. A quantity limit of two tubes (120 gams total) per 28-day supply should be sufficient or better for the majority of patients to utilize this therapy. Upon initial trial of medication, quantity limits will be set at two tubes per 28-day supply to ensure appropriate utilization within FDA label (e.g., non-continuous use), as well as ensure patients realize efficacy with medication and to minimize medication waste in the event therapy is not effective.

XXI. Ruxolitinib (Opzelura) was evaluated in two phase 3, randomized, double-blind, vehicle-controlled studies in 674 adolescents and adults (TRuE-V1 and TRuE-V2) age 12 and older. Treatment arms: vehicle, ruxolitinib 1.5%. Subjects were randomized 2:1 of ruxolitinib to vehicle and used continuously twice a day for 24 weeks, then an additional 28 week extension where all subjects received ruxolitinib twice daily. Trial population characteristics included: At least 12 years of age, 53% were female, 82% were white, had mean depigmented areas of 1% F-BSA,

mean affected total BSA of up to 7.4%, median duration of nonsegmental vitiligo of 14.8 years, and subjects were not permitted to use phototherapy during the trial period.

XXII. The primary endpoint for both trials was percent of patients to achieve decrease of at least 75% from baseline in the facial vitiligo area scoring index (F-VASI: takes into account level of depigmentation and lesion integrity) at week 24. Secondary endpoints included decrease of at least 50% in F-VASI, a decrease of at least 90% in F-VASI, decrease of 50% in total vitiligo area scoring index (T-VASI), change in VNS rating, and percentage change of total facial BSA affected.

XXIII. The adverse events (AE) at week 24 were similar across both treatment groups, with the most common AE related to the trial drug were acne (5.4%) and pruritis (5.0%). Discontinuation rates from AE were <1%. Additional reporting of safety data after the extension period (week 52) found no additional safety concerns. AEs were similar to AEs noted in atopic dermatitis studies. There were 14 cases of serious AEs: 8 in the TRuE-V1 and 6 in the TRuE-V2. Review of supplemental data indicates most AEs resolved and no direct correlation to use of medication. 3 serious AEs that are ongoing include a subacute cord degeneration, prostate cancer, and papillary thyroid cancer. Overall, the two trials indicated improvement in the endpoints, there is still uncertainty in place of therapy, safety and efficacy in combination with other topical therapies for vitiligo, long term safety and efficacy against other topical agents. The safety and efficacy profiles of other topical therapies are well established, and data are lacking to show superior safety and efficacy of ruxolitinib (Opzelura) over these agents. There is a lack of safety and efficacy data in pediatric patients under 12 years of age and other topical therapies have been approved in this age group. There are ongoing extension studies assessing long term safety and efficacy past 52 weeks for 12 years of age and up but as of this time, it is not being evaluated for patients younger than 12 years of age with vitiligo.

XXIV. According to AAD guidelines, TCIs may be preferable to TCS in patients with recalcitrance to steroids, sensitive areas involved, steroid-induced atrophy, and long-term uninterrupted topical steroid use.

XXV. Treatment for moderate to severe disease includes the same topical classes noted above and, for those not amenable to topical, systemic immunosuppressants (e.g., corticosteroids, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil), JAK inhibitors (e.g., abrocitinib, upadacitinib), and dupilumab (Dupixent), a biologic IgG4 that is FDA-approved for pediatrics and adults as a biologic option for moderate-to-severe atopic dermatitis. Currently, there are no head to head trials evaluating safety and/or efficacy differences or superiority between biologic therapies in atopic dermatitis. Dupilumab (Dupixent) has an established safety and efficacy profile for the treatment of atopic dermatitis and is approved down to six years of age. Upadacitinib (Rinvoq) has been evaluated and is FDA approved in patients down to 12 years of age. Abrocitinib (Cibinqo) is FDA approved in adult patients only.

XXVI. There may be patient specific scenarios in which the use of additional topical agents following failure of one class of topical agents would be impractical. Insight from dermatology specialists indicate that patients who have at least 15% BSA involvement, or involvement in sensitive areas (e.g., eyelids, axilla, genitals, gluteal cleft), and have severe disease are potential candidates for systemic biologic therapy. Severe disease, as defined by NICE guidelines, includes widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking, and alteration of pigmentation), and severe limitation of everyday activities and psychosocial functioning, nightly loss of sleep; severe disease can also be

classified as physician's global assessment (PGA) score of 4.0. Additionally, administration of topical agents may become impractical for patients with high disease burden (BSA ≥ 20%), considering twice daily administration is necessary for non-steroid topical agents for optimal efficacy.

Investigational or Not Medically Necessary Uses

I. Ruxolitinib (Jakafi, Opzelura) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Low risk myelofibrosis
   B. Acute leukemia
   C. COVID-19 or associated symptoms or complications
   D. Alopecia areata
   E. Other vitiligo diseases outside of nonsegmental or other depigmentation disease
   F. Glioma and glioblastoma
   G. Hidradenitis suppurativa
   H. Cancer or malignancy outside of myelofibrosis

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Jakafi [Prescribing Information]. Incyte Corporation. Wilmington, DE. May 2019.
2. Opzelura [Prescribing Information]. Incyte Corporation. Wilmington, DE. September 2021.
3. Verstovsek, S, Mesa, RA, Gotlib, J, et al. Efficacy, safety and survival with ruxolitinib in patients with myelofibrosis: results of a median 2-year follow-up of COMFORT-I. Italy, 2013. p. 1865-71.
4. Verstovsek, S, Mesa, RA, Gotlib, J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. The New England journal of medicine. 2012 Mar 1;366(9):799-807. PMID: 22375971
5. Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. N Engl J Med. 2015;372(5):426-435. [PubMed 25629741]
6. Mesa RA, Gotlib J, Gupta V, et al. Effect of ruxolitinib therapy on myelofibrosis-related symptoms and other patient-reported outcomes in COMFORT-I: a randomized, double-blind, placebo-controlled trial. J Clin Oncol. 2013;31(10):1285-1292. [PubMed 23423753]
7. Verstovsek S, Mesa RA, Gotlib J, et al. Long-term treatment with ruxolitinib for patients with myelofibrosis: 5-year update from the randomized, double-blind, placebo-controlled, phase 3 COMFORT-I trial. J Hematol Oncol. 2017;10.
8. Jagasia M, Perales M-A, Schroeder MA, et al. Ruxolitinib for the treatment of steroid-refractory acute GVHD (Reach1): a multicenter, open-label phase 2 trial. Blood. 2020;135(20):1739-1749.
9. Wu H, Shi J, Luo Y, et al. Evaluation of Ruxolitinib for Steroid-Refractory Chronic Graft-vs-Host Disease After Allogeneic Hematopoietic Stem Cell Transplantation. JAMA Netw Open. 2021;4(1):e2034750. doi:10.1001/jamanetworkopen.2020.34750.
10. American Academy of Dermatology – Guidelines of Care for the Management of Atopic Dermatitis (2014). Available at: https://www.aad.org/member/clinical-quality/guidelines/atopic-dermatitis
11. Eichenfield L., Tom, W., Chamlin S., et al. Guidelines of care for the management of atopic dermatitis. JAAD. 2014 Feb 1. 70(2): 338-351.

12. Clinical Review Report: Dupilumab (Dupixent): (Sanofi-Aventis Canada Inc.): Indication: Moderate-to-severe atopic dermatitis (AD) [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2018 Jul. Appendix 5, Validity of Outcomes Measures. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539234/
13. Rosmarin D, Passeron T, Pandya AG, et al.; TRuE-V Study Group. Two Phase 3, Randomized, Controlled Trials of Ruxolitinib Cream for Vitiligo. N Engl J Med. 2022 Oct 20;387(16):1445-1455. doi: 10.1056/NEJMoa2118828. PMID: 36260792.
14. leftheriadou, V., Atkar, R., Batchelor, J., et al. and (2022), British Association of Dermatologists guidelines for the management of people with vitiligo 2021*. Br J Dermatol, 186: 18-29. https://doi.org/10.1111/bjd.20596
15. American Academy of Dermatology – Vitiligo: Diagnosis and Treatment. Available at: https://www.aad.org/public/diseases/a-z/vitiligo-treatment
16. Dupixent [Prescribing Information]. Regeneron Sanofi Genzyme. Tarrytown, NF. May 2020.
17. Protopic [Prescribing Information]. Astellas Pharma US, Inc. Deerfield, IL. November 2011.
18. Elidel {Prescribing Information]. Novartis Pharmaceuticals Corp. East Hanover, NJ. January 2006.
19. Eucrisa [Prescribing Information]. Pfizer Labs. New York, NY. April 2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added criteria for nonsegmental vitiligo	12/2022
Added ruxolitinib cream (Opzelura) policy criteria and supportive evidence for use in nonsegmental vitiligo. Updated E/I to reflect removal of nonsegmental vitiligo and maintain others as excluded.	11/2022
Added new indication of nonsegmental vitiligo for Opzelura noting this is an excluded indication.	09/2022
Ruxolitinib cream added into the policy for the treatment of atopic dermatitis.	08/2021
Chronic graft vs. host disease indication added to policy. Update of qualifying prescribers and appropriate doses and quantities per indication. Removal of infection free requirement, check of unacceptable toxicity, and requirement for previous use of hydroxyurea in myelofibrosis.	06/2021
Addition of acute graft vs. host disease indication to renewal section.	01/2020
Criteria transitioned to policy. Added newly FDA approved indication of acute graft versus host disease. Remove diagnostic questions, interaction questions, lab value questions. Added requirement for previous use of hydroxyurea prior to coverage of Jakafi for the indication of polycythemia vera.	07/2019
Previous reviews	12/2014, 12/2012, 07/2012, 05/2012

Policy Type: PA/SP Pharmacy Coverage Policy: UMP209

Description

Satralizumab-mwge (Enspryng) is an IL-6 monoclonal antibody subcutaneous injection.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
satralizumab (Enspryng)	120 mg/mL Prefilled Syringe	Neuromyelitis optica spectrum disorder (NMOSD)	**Initial**: 2 mL (pens) per 28 days for one fill **Maintenance**: 1 mL (pen) per 28 days

Initial Evaluation

I. Satralizumab (Enspryng) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a neurologist; **AND**
   C. Provider attestation the medication will not be used in combination with other biologic therapies (e.g., tocilizumab [Actemra], eculizumab [Soliris], inebilizumab [Uplinza]) used to treat inflammatory conditions; **AND**
   D. Documentation of a confirmed diagnosis of **neuromyelitis optica spectrum disorder (NMOSD)** when all of the following are met:
      1. The member is positive for anti-aquaporin-4 (AQP4) IgG antibodies (i.e., seropositive) supported by chart note documentation or laboratory results; **AND**
      2. The member has a history of one or more relapses requiring rescue or acute treatment (e.g., glucocorticoids, plasma exchange); **AND**
      3. Glucocorticoids, azathioprine, and/or mycophenolate will be used in combination with satralizumab (Enspryng); **OR**
         i. Treatment with ALL of the following has been ineffective, contraindicated, or not tolerated for long term maintenance therapy:
            i. Glucocorticoids
            ii. azathioprine
            iii. mycophenolate; **AND**

4. Treatment with rituximab (e.g. Rituxan) has been ineffective, contraindicated, or not tolerated

II. Satralizumab (Enspryng) is considered not medically necessary when criteria above are not met and/or when used for:
   A. NMOSD that is anti-quaporin-4 (AQP4) IgG antibody negative (i.e., seronegative)

III. Satralizumab (Enspryng) is considered investigational when used for all other conditions, including but not limited to:
   A. Rheumatoid or other forms of arthritis
   B. Cytokine release syndrome
   C. Arteritis

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication is prescribed by, or in consultation with, a neurologist; **AND**
IV. Provider attestation the medication will not be used in combination with other biologic therapies (e.g., tocilizumab [Actemra], eculizumab [Soliris], inebilizumab [Uplinza]) used to treat inflammatory conditions; **AND**
V. Provider attestation of a positive response to therapy (e.g., stabilization of disease, relapse reduction, relapse-free)

Supporting Evidence

I. Satralizumab (Enspryng) is FDA-approved for NMOSD, a rare inflammatory disorder characterized by severe, immune-mediated attacks on the optic nerves and spinal cord. Hallmark features include optic neuritis attacks, transverse myelitis, unexplained hiccups, nausea, vomiting, and somnolence. Patients experience relapses that have varying degrees of recovery over weeks to months. NMOSD was historically considered as a form of multiple sclerosis (MS); however, MS therapies are often inefficacious in the setting of NMOSD and certain MS therapies may further exacerbate NMOSD. Thus, a definitive diagnosis from a specialty provider is warranted. The majority of patients are seropositive, and if test results show seronegative disease, patients should be retested or considered for a differential diagnosis. Seronegative disease is often treated similarly to seropositive NMOSD; however, biologic medications often lack efficacy in the seronegative population.
II. NMOSD is often treated acutely with high-dose IV glucocorticoids, and if refractory – plasma exchange. Once a definitive diagnosis is made, long-term therapy is recommended in all patients. Long-term therapies that are FDA-approved include eculizumab (Soliris) and inebilizumab (Uplinza), which are both provider administered products. Other therapies that

have been used historically and are often regarded as standard of care include glucocorticoids, azathioprine, mycophenolate, and rituximab (e.g., Rituxan). Additionally and increasingly, IV tocilizumab (Actemra) has been considered. The quality of data varies for these agents; however, all have shown positive response on relapse rates for seropositive NMOSD. The safety profile, is also further defined, given the longevity and extent of use in patients relative to satralizumab (Enspryng).

III. The efficacy and safety of satralizumab (Enspryng) was evaluated in two Phase 3, blinded, randomized, placebo-controlled trials, where treatment was administered at weeks zero, two, four, then four weeks thereafter. Population characteristics: seropositive and negative patients, majority female, an annualized relapse rate of 1.5 with at least one documented attack in the last 12 months, with a variety of treatment histories (e.g., glucocorticoids [GC], DMARDS, previous b-cell depleting therapy). Exclusions: history of anti-IL-6 therapy, alemtuzumab, total body irradiation, or bone marrow transplantation.

IV. Trial one evaluated satralizumab (Enspryng) monotherapy versus placebo, and trial two evaluated against placebo with both groups adding treatment to background immunosuppressive therapy (glucocorticoids, mycophenolate, azathioprine, and various combinations). The use of satralizumab (Enspryng) in addition to other biologic therapies (e.g., tocilizumab [Actemra], eculizumab [Soliris], inebilizumab [Uplinza]) has not been evaluated for safety and/or efficacy. Additionally, there is evidence to show that use of two biologic therapies concurrently has demonstrated increased risk of serious infection.

V. Adolescent patients were included in the second pivotal trial, ages 12 and older. There was a low number (n=7) enrolled and subgroup analyses did not show clinical efficacy. Although this analysis was likely underpowered, safety and efficacy in non-adult population remains unknown at this time and FDA-approval has been granted for adults only.

VI. In both trials there was a positive response on relapse rates in the seropositive (anti-aquaporin-4 [AQP4) antibody-positive) population. Of note, there was a lack of statistically significant efficacy in the seronegative population. Secondary outcomes evaluated medication efficacy on other symptom control, quality of life, and caregiver burden; however, they were not statistically significant. Medication success may be measured as a reduction in or freedom from relapses.

Investigational or Not Medically Necessary Uses

I. Satralizumab (Enspryng) did not show improvement in relapse rates in the seronegative NMOSD population. Given lack of efficacy and largely unknown safety profile for this therapy, use is not medically necessary at this time.

II. Satralizumab (Enspryng) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
    A. Rheumatoid or other forms of arthritis
    B. Cytokine release syndrome
    C. Arteritis
        i. IL-6 therapies (e.g., tocilizumab [Actemra] have been FDA-approved for the conditions listed above; however, use of satralizumab (Enspryng) for these conditions remains experimental and investigational.

References

1. Traboulsee A, Greenberg BM, Bennett JL, et al. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder: a randomised, double-blind, multicentre, placebo-controlled phase 3 trial. Lancet Neurol. 2020;19(5):402-412.
2. Yamamura T, Kleiter I, Fujihara K, et al. Trial of Satralizumab in Neuromyelitis Optica Spectrum Disorder. N Engl J Med. 2019;381(22):2114-2124.
3. Enspryng [Prescribing Information]. Genentech, Inc. San Francisco, CA. August, 2020.
4. Collongues N, Ayme-dietrich E, Monassier L, De seze J. Pharmacotherapy for Neuromyelitis Optica Spectrum Disorders: Current Management and Future Options. Drugs. 2019;79(2):125-142.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP081

Split Fill Management (Only Applies to enzalutamide [Xtandi], and abiraterone [Zytiga, Yonsa])*

Description

Darolutamide (Nubeqa), apalutamide (Erleada), and enzalutamide (Xtandi) are orally administered androgen receptor inhibitors. Abiraterone (Zytiga, Yonsa) is an androgen biosynthesis inhibitor of CYP17.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
darolutamide (Nubeqa)	Prostate cancer, non-metastatic, castration resistant Prostate cancer, metastatic, castration-sensitive	300 mg tablets	120 tablets/30 days
apalutamide (Erleada)	Prostate cancer, non-metastatic, castration resistant	60 mg tablets	
	Prostate cancer, metastatic, castration-sensitive	240 mg tablets	30 tablets/30 days
enzalutamide (Xtandi)	Prostate cancer, castration resistant	40 mg capsules	120 capsules/30 days
	Prostate cancer, metastatic, castration-sensitive	40 mg tablets	120 tablets/30 days
	Prostate cancer, non-metastatic, castration sensitive	80 mg tablets	60 tablets/30 days
abiraterone (Yonsa)	Prostate cancer, metastatic, castration-resistant, in combination with methylprednisolone	125 mg tablets	120 tablets/30 days
abiraterone (generic Zytiga)	Prostate cancer, metastatic, castration-resistant, in combination with prednisone	250 mg tablets	120 tablets/30 days
	Prostate cancer, metastatic, castration-sensitive, in combination with prednisone	500 mg tablets	60 tablets/30 days
abiraterone (Zytiga)		250 mg tablets	120 tablets/30 days
	Prostate cancer, non-metastatic, castration sensitive, in combination with prednisone	500 mg tablets	60 tablets/30 days

Initial Evaluation

I. **Darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), or abiraterone (Zytiga, Yonsa)** may be considered medically necessary when the following criteria below are met:
   A. The member is 18 years of age or older; **AND**
   B. The medication is prescribed by, or in consultation with, an oncologist or urologist; **AND**
   C. The member has **not** previously progressed on darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), OR abiraterone (Zytiga, Yonsa); **AND**
   D. Darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), or abiraterone (Zytiga, Yonsa) will **not** be used in combination with any other oncolytic medication with the exception of therapies outlined below (e.g., hormone suppression therapy, docetaxel for mCSPC, or PARP inhibitors [i.e., olaparib (Lynparza) and talazoparib (Talzenna)] for mCRPC); **AND**
   E. The member has either had a bilateral orchiectomy OR ongoing hormone suppression (e.g., GnRH therapy) will be used concurrently; **AND**
   F. A diagnosis of one of the following:
      1. **Non-metastatic castration resistant prostate cancer**, defined by evidence of disease progression despite therapy with a gonadotropin-releasing hormone analog (GnRH) or a bilateral orchiectomy; **AND**
         i. The member has a PSA-doubling time of 10 months or less during continuous androgen-deprivation therapy or after bilateral orchiectomy; **AND**
         ii. One of the following is prescribed: darolutamide (Nubeqa), apalutamide (Erleada), OR enzalutamide (Xtandi); **OR**
      2. **Non-metastatic castration sensitive prostate cancer; AND**
         i. The member is in the high- or very high-risk group defined by:
            a. Node positive; **OR**
            b. Node negative; **AND**
               i. The member has two of the following:
                  1. Stage T3 or T4 tumor
                  2. Gleason Score ≥ 8
                  3. PSA ≥ 40 ng/mL; **OR**
            c. Experienced PSA doubling time of <6 months or PSA concentration ≥20 ng/mL on androgen deprivation therapy (e.g. GnRH analogs); **AND**
         ii. The request is for generic abiraterone 250 mg tablets and will be used in combination with ALL the following:
            a. External beam radiotherapy (EBRT), unless contraindicated
            b. Androgen deprivation therapy (ADT) (e.g. GnRH analogs)
            c. Prednisone; **OR**
         iii. The request is for generic abiraterone 500 mg tablets or brand abiraterone (Zytiga, Yonsa); **AND**
            a. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); **AND**

b. Treatment will be used in combination with EBRT (unless contraindicated), ADT, and prednisone**; OR**

iv. The request is for enzalutamide (Xtandi); **AND**

a. Documentation of intolerance or contraindication to generic abiraterone; **OR**

3. **Metastatic castration resistant prostate cancer**, defined by evidence of disease progression despite therapy with a gonadotropin-releasing hormone analog (GnRH) or a bilateral orchiectomy; **AND**

i. The request is for generic abiraterone 250 mg tablets and will be used in combination with prednisone; **OR**

ii. The request is for generic abiraterone 500 mg tablets; **AND**

a. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); **OR**

iii. The request is for brand abiraterone (Zytiga), brand abiraterone (Yonsa); **AND**

a. Documentation of intolerance or contraindication to generic abiraterone; **AND**

b. Will be used in combination with prednisone; **OR**

iv. The request is for enzalutamide (Xtandi); **AND**

a. Medication will be used as monotherapy **AND**

i. Documentation of intolerance or contraindication to generic abiraterone; **OR**

b. Enzalutamide (Xtandi) will be used in combination with talazoparib (Talzenna); **AND**

i. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) alteration in BRCA1 or BRCA2 gene; **AND**

1. Documentation of intolerance or contraindication to generic abiraterone in combination with olaparib (Lynparza); **OR**

ii. The member has an alteration in an HRR gene that is not BRCA1 or BCRA2 (e.g., *ATM, ATR, CDK12*, etc.); **OR**

4. **Metastatic castration sensitive or castration naïve prostate cancer; AND**

i. **For generic abiraterone:**

a. The member has at least TWO of the following risk factors:

i. Gleason Score ≥ 7 (Grade Group ≥ 2)

ii. Bone lesions

iii. Presence of measurable visceral metastases; **AND**

b. Abiraterone will be used in combination with prednisone; **AND**

i. If used in combination with docetaxel, the provider attests that the member has high-volume metastatic burden; **AND**

c. The request is for generic abiraterone 250 mg tablets; **OR**

i. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); **OR**

ii. **For BRAND abiraterone (Zytiga), apalutamide (Erleada), darolutamide (Nubeqa), or enzalutamide (Xtandi):**
   a. The member has at least TWO of the following risk factors:
      i. Gleason Score ≥ 7 (Grade Group ≥ 2)
      ii. Bone lesions
      iii. Presence of measurable visceral metastases; **AND**
   b. The member must have had an inadequate response, intolerance, or contraindication to generic abiraterone (Note: if criteria is met for generic abiraterone, use of the 250 mg tablets will be required); **AND**
   c. If the request is for abiraterone (Zytiga), it will be used in combination with prednisone; **AND**
      i. If used in combination with docetaxel, the provider attests that the member has high-volume metastatic burden; **OR**
   d. If the request is for darolutamide (Nubeqa), it will be used in combination with docetaxel

II. Darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), and abiraterone (Zytiga, Yonsa) are considered investigational when used for all other conditions, including but not limited to:
   A. Cushing's Syndrome
   B. Breast cancer
   C. Hepatocellular carcinoma
   D. Fallopian tube, ovarian, or uterine cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. The medication is prescribed by, or in consultation with, an oncologist or urologist; **AND**
IV. Darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), or abiraterone (Zytiga, Yonsa) will **not** be used in combination with any other oncolytic medication with the exception of docetaxel for mCSPC or PARP inhibitors [i.e., olaparib (Lynparza) and talazoparib (Talzenna)] for mCRPC; **AND**
V. The member has either had a bilateral orchiectomy OR ongoing hormone suppression (e.g., GnRH therapy) will be used concurrently; **AND**
VI. The member has experienced a response to therapy (e.g., stabilization of disease, decrease in tumor size or tumor spread, lack of disease progression); **AND**
   1. **Non-metastatic castration resistant prostate cancer;**

i. The request is for one of the following: darolutamide (Nubeqa), apalutamide (Erleada), OR enzalutamide (Xtandi); **OR**

2. **Non-metastatic castration sensitive prostate cancer; AND**
   i. The request is for generic abiraterone 250 mg tablets and will be used in combination with prednisone, EBRT (unless contraindicated), and a GnRH analog; **OR**
   ii. The request is for abiraterone 500mg tablets or brand abiraterone (Zytiga, Yonsa); **AND**
      a. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); **AND**
      b. Treatment will be used in combination with EBRT (unless contraindicated), ADT, and prednisone**; OR**
3. **Metastatic castration resistant prostate cancer;**
   i. The request is for generic abiraterone 250 mg tablets and will be used in combination with prednisone; **OR**
   ii. The request is for generic abiraterone 500 mg tablets; **AND**
      a. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); **OR**
   iii. The request is for brand abiraterone (Zytiga) plus prednisone OR brand abiraterone (Yonsa) plus methylprednisolone; **AND**
      a. The member has an intolerance or contraindication to generic abiraterone (use of 250 mg tablets required); **OR**
   iv. The request is for enzalutamide (Xtandi); **OR**
4. **Metastatic castration sensitive prostate cancer;**
   i. The request is for generic abiraterone 250 mg tablets and will be used in combination with prednisone; **OR**
      a. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); **OR**
   ii. The request is for enzalutamide (Xtandi), darolutamide (Nubeqa), or apalutamide (Erleada); **OR**
   iii. The request is for brand abiraterone (Zytiga); **AND**
      a. The member has had inadequate response, intolerance, or contraindication to generic abiraterone (use of 250 mg tablets required); **AND**
      b. Will be used in combination with prednisone

Supporting Evidence

I. Prostate cancer therapies have been evaluated for safety and efficacy in adults. There are multiple treatment modalities with the direction of therapy depending on the manifestations of the disease. The initial and continued approach should be directed by a specialist due to the

nuances of treatment, monitoring of disease, treatment safety, evaluation of efficacy, and consideration for patient specific goals.

II. Many treatment options exist, and initial and further line therapy are contingent upon patient specific characteristics. These options include, but are not limited to, radiation therapy, prostatectomy, androgen deprivation pharmacotherapy, bilateral orchiectomy, chemotherapy, abiraterone (Zytiga, Yonsa), or androgen receptor inhibitors (e.g., enzalutamide (Xtandi), darolutamide (Nubeqa), apalutamide (Erleada)). Multi-modal therapy, such as abiraterone or enzalutamide with ADT, is commonly utilized; however, abiraterone and/or androgen receptor inhibitor combinations have not been evaluated for safety and efficacy to date. Continuation of ADT is commonly employed and is recommended as concomitant therapy as discontinuation of GnRH agonists are likely to result in an increase in serum testosterone and disease progression.

III. Use of androgen receptor inhibitor (e.g., darolutamide [Nubeqa], apalutamide [Erleada], enzalutamide [Xtandi]) therapy after disease progression on abiraterone, or vice versa (i.e., abiraterone/androgen receptor inhibitor crossover therapy), has not yet been evaluated for safety and efficacy in quality clinical trials. One retrospective trial evaluating enzalutamide after treatment with abiraterone showed that very few patients (10% or less) had a significant decrease in PSA with enzalutamide therapy. A retrospective case series showed a similar lack of efficacy in regard to abiraterone after enzalutamide (Xtandi). Additionally, there are studies to suggest cross resistance in switching between second generation anti-androgens. It has been demonstrated that there is a cross-resistance mechanism between darolutamide, apalutamide, enzalutamide, and abiraterone. NCCN guidelines note evidence-based guidance on the sequencing of ADT agents remains limited.

IV. **Non-metastatic castration resistant prostate cancer:** darolutamide (Nubeqa), apalutamide (Erleada), and enzalutamide (Xtandi) are the androgen receptor inhibitors that have been evaluated in this stage of disease. Concurrent treatment with steroids is not required. Patients in the trials for each of these medications had a prostate-specific antigen doubling time of 10 months or less and received GnRH therapy concurrently. Each therapy was evaluated in a double-blind, placebo-controlled trial.

- Darolutamide (Nubeqa) was evaluated in the ARAMIS TRIAL. The primary outcome, metastasis free survival (MFS), showed a statistical significance over placebo (40 vs 18 months, $p<0.001$). Apalutamide (Erleada) was evaluated in the SPARTAN trial, MFS was statistically significant compared to placebo (40 vs 16 months), and enzalutamide (Xtandi) was evaluated in the PROSPER trial. The MFS was significant compared to placebo (37 months vs 15 months).
- Darolutamide (Nubeqa) does not cross the blood brain barrier; thus, may offer an improved safety profile compared to enzalutamide and even apalutamide (Erleada). There were low rates of fatigue, falls, fractures, and seizures; however, head-to-head trials have not yet been conducted and caution should be used when comparing across trials to make treatment decisions.

V. **Non-metastatic castration sensitive prostate cancer:** abiraterone in combination with androgen deprivation therapy (ADT) (e.g. GnRH analogs) and prednisone, was evaluated in a phase III, randomized, open-label study (STAMPEDE) with 1974 participants with high-risk, non-metastatic prostate cancer. Participants were considered high risk if they are node positive alone, if they are node negative with two factors (stage T3 or T4, Gleason Score >8, or PSA >40), or if there

was disease progression on ADT (defined by a PSA ≥ 4ng/mL with a doubling time of <6 months, or PSA ≥ 20 ng/mL). Radiotherapy was required for those participants with node negative and highly encouraged for those that were node positive. A total of 99% of participants with node negative and 77% of participants with node positive disease received radiotherapy (overall 85%). The primary outcome of metastasis-free survival (MFS) was significantly longer in the combination-therapy group versus ADT alone and 6-year MFS improved from 69% in the ADT groups to 82% in the combination therapy groups (HR 0·53, 95% CI 0·44–0·64; p<0·0001). There was a total of 147 deaths in the combination group compared to 236 in the ADT group – overall survival was significantly longer in the combination group vs ADT (not reached, 103–NE; HR 0·60, 95% CI 0·48–0·73, p<0·0001). Prostate-cancer-specific survival was significantly improved in the combination- therapy groups versus ADT alone (HR 0·49, 95% CI 0·37–0·65, p<0·0001). The most common ADE in combination group versus ADT was hypertension (393 (41%) vs 153 (5%)), aminotransaminases (332 (34%) vs 136 (14%)).

VI. Enzalutamide (Xtandi) received FDA approval for treatment of non-metastatic, castration sensitive prostate cancer, with or without GnRH analog. Enzalutamide in combination with leuprolide, enzalutamide monotherapy and placebo plus leuprolide, was evaluated in a Phase III, randomized, double-blinded, study (EMBARK) with 1068 participants with high-risk, non-metastatic prostate cancer. Participants were considered high risk if they are node positive or had a PSA doubling time less than 9 months after EBRT. The primary outcome of metastasis-free survival (MFS) between the combination group vs leuprolide alone was evaluated. MFS was significantly longer in the combination-therapy group versus placebo and leuprolide (HR 0.42, 95% CI, 0.30-0.61, p<0.0001). The 5-year metastasis-free survival was 87.3% (95% confidence interval [CI], 83.0 to 90.6) in the combination group and 71.4% (95% CI, 65.7 to 76.3) in the leuprolide-alone group. Secondary analysis also demonstrated that enzalutamide monotherapy was also superior to leuprolide alone in delaying metastasis or death (HR 0.63; 95% CI, 0.46-0.87, P=0.005). The most common adverse event leading to discontinuation was fatigue (in 12 patients [3.4%] in the combination group, 4 patients [1.1%] in the leuprolide-alone group, and 8 patients [2.3%] in the monotherapy group).
    - NCCN prostate cancer guidelines provide a category 2a recommendation for use of abiraterone acetate in combination with prednisone, EBRT, and ADT in those categorized as high or very high risk, and such combination is listed as the preferred treatment. As of January 2024, NCCN guidelines have not been updated to include enzalutamide (Xtandi)'s new indication.
    - Contraindications to EBRT include, but are not limited to preexisting anal fistula, inflammatory bowel disease (e.g. ulcerative colitis, diverticulitis, etc.), unacceptable operative risks or medically unsuitable for anesthesia, history of previous pelvic radiotherapy, and ataxia telangiectasia.

VII. **Metastatic, castration resistant prostate cancer:** enzalutamide (Xtandi) and abiraterone (Zytiga, Yonsa) have been evaluated for safety and efficacy. Enzalutamide (Xtandi) versus placebo was evaluated in those that had previously been treated with chemotherapy and those that were chemotherapy naïve. Overall survival was prolonged in both settings. Abiraterone (Zytiga, Yonsa) plus prednisone has also shown prolonged survival in this setting in those that have been previously treated with chemotherapy and those chemotherapy naïve. Head-to-head trials have not been completed to provide insight to superior therapy between abiraterone (Zytiga, Yonsa)

and enzalutamide (Xtandi). Abiraterone (Zytiga, Yonsa) is indicated in combination with prednisone; however, enzalutamide has safety concerns including CNS toxicities and seizures. Additionally, abiraterone (Zytiga, Yonsa) has generic availability.

- The combination therapy of enzalutamide (Xtandi) and talazoparib (Talzenna) was evaluated in the TALAPRO-2 trial. Talazoparib (Talzenna) is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes. A total of 805 patients were randomized 1:1 to either receive talazoparib/enzalutamide or placebo/enzalutamide. They were further stratified by previous novel hormonal therapy/docetaxel and HRR gene-alteration status. The primary outcome was radiographic progression free survival (rPFS) assessed by blinded independent central review per RECIST 1.1 (soft tissue disease) and Prostate Cancer Clinical Trials Working Group 3 (bone disease). Treatment with talazoparib/enzalutamide resulted in a 37% lower risk of radiographic progression or death compared to placebo plus enzalutamide (HR 0·63; 95% CI 0·51–0·78; p<0.0001). The most common adverse effects in the treatment group were anemia (66%), neutropenia (36%), and fatigue (34%).
- In a randomized, double-blind, Phase 3 clinical trial (PROpel), the efficacy, safety, and tolerability of olaparib (Lynparza) was assessed versus placebo when given in addition to abiraterone in men with metastatic castration-resistant prostate cancer (mCRPC), who had not received prior chemotherapy or novel hormonal agents (NHAs; e.g., enzalutamide, apalutamide, abiraterone) in the 1st-line metastatic setting. Previous therapy with docetaxel in the neoadjuvant or adjuvant setting, as well as first-generation antiandrogen agents (e.g., bicalutamide, nilutamide) were permitted; however, were not required as part of the inclusion criteria. The primary endpoint, radiographic progression-free survival (rPFS), and secondary endpoints included OS and time to first subsequent anticancer therapy or death. In a predefined interim analysis (as of July 2022), olaparib (Lynparza) in combination with abiraterone reduced the risk of disease progression or death by 34% versus abiraterone alone (based on a hazard ratio [HR] of 0.66; 95% confidence interval [CI] 0.54-0.81; p<0.0001). Median rPFS was 24.8 months for olaparib (Lynparza) plus abiraterone versus 16.6 months for abiraterone alone.
- As of 9/2023, there are no head-to-head trials suggesting superiority of one PARP inhibitor/antiandrogen combination therapy over another. Both olaparib/abiraterone and talazoparib/enzalutamide are categorized as useful in certain circumstances with a Category 1 recommendation per NCCN guidelines. olaparib/abiraterone was FDA approved for this indication in patients harboring a *BRCAm*, while talazoparib/enzalutamide carries a broader FDA approval encompassing all *HRRm*. DNA repair anomalies known as homologous recombination repair gene mutations (HRRm) are identified in approximately 25% of patients with mCRPC. HRR gene mutations can consist of mutations in *ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, or RAD51C*. Approximately 10-15% of patients with mCRPC have the BRCA1/BRCA2 gene mutations. These mutations have been associated with more aggressive disease and poor patient outcomes.

VIII. **Metastatic high-risk castration sensitive prostate cancer:** abiraterone (Zytiga, Yonsa) plus prednisone has been evaluated for safety and efficacy. High risk disease was defined as having at least two of the following three risk factors: Gleason score eight or greater, presence of three or more bone lesions, evidence of measurable visceral metastases. Overall survival over placebo was shown to be statistically significant for abiraterone (Zytiga, Yonsa).

- NCCN prostate cancer guidelines provide a category 1 recommendation for use of abiraterone acetate in combination with docetaxel and ADT in those with a high-volume metastatic burden who are candidates for chemotherapy. This is based on the findings from the PEACE-1 clinical trial, which evaluated the safety and efficacy of standard of care (SOC) therapy, defined as docetaxel and ADT, against SOC plus abiraterone acetate and prednisone. The co-primary endpoint consisted of radiographic progression free survival (rPFS) and overall survival (OS). The abiraterone group demonstrated statistically significant benefit in rPFS and OS with a hazard ratio (HR) was 0.50 (99.9% CI 0.34-0.71; p<0.0001) and 0.75 (95.1% CI 0.59-0.95; p=0.017), respectively. However, further analysis based on volume of metastatic burden revelated that OS was only statistically significant in the population with high-volume metastatic burden (HR 0.72 [95.1% CI 0.55-0.95]; p=0.019) compared to low-volume metastatic burden (HR 0.83 [95.1% CI 0.50-1.39]; p=0.66). According to NCCN, high-volume disease is differentiated from low-volume disease by visceral metastases and/or four or more bone metastases, with at least one metastasis beyond the pelvis vertebral column. While the addition of docetaxel to abiraterone acetate and ADT did increase overall incidence of adverse reactions, it did not increase the incidence of severe or fatal adverse events and the safety profile is largely the same. Docetaxel is intended to be used at the same time or within a few weeks of starting therapy with darolutamide or abiraterone. In mHSPC, docetaxel is dosed on every 3-week cycles for a total of 6 cycles; completion of docetaxel therapy should reasonably be able to occur within the initial approval period of 6 months.

IX. Although both strengths (250 mg and 500 mg) of abiraterone (Zytiga) are available in generic formulations, the 500 mg tablet remains at a significantly higher cost (40x greater) than the 250 mg tablet. Thus, use of generic abiraterone 250 mg is required over abiraterone 500 mg tablet.

X. Apalutamide (Erleada) was evaluated in the metastatic, castration sensitive prostate cancer setting in combination with ADT versus ADT alone. This was not specifically in high-risk disease; however, 93% of subjects had a Gleason Score of seven or greater, and all subjects had bone metastases. Fifty-five percent of subjects had bone only metastases, and the remaining had additional metastases. Primary outcomes were radiographic progression free survival, which were statistically and clinically significant favoring apalutamide (Erleada). Head-to-head trials against abiraterone (Zytiga) have not occurred in this setting; however, the safety profile of abiraterone is further established at this time.

XI. Enzalutamide (Xtandi) was evaluated in metastatic, castration sensitive, prostate cancer in combination with ADT versus ADT alone. This study was not specifically in high-risk disease; however, the majority of subjects (> 67%) had a Gleason score of 8 or greater – nearly 85% had bone metastases or bone and other metastases. Progression-free survival was 19 months for placebo plus ADT and was not reached for enzalutamide (Xtandi). Radiographic progression was

experienced by 13.8% of those receiving enzalutamide (Xtandi) and 32.6% for placebo plus ADT. Head-to-head trials against abiraterone have not occurred in this setting; however, abiraterone provides a better value for the treatment of mCSPC at this time. Additionally, enzalutamide (Xtandi) was evaluated in a Phase III open-label trial in addition to ADT versus ADE alone in those that were castration naïve. The primary endpoint of OS was statistically significant in a group of 125 subjects (HR for death: 0.67, CI 0.52-0.86, p=0.002).

XII. Darolutamide (Nubeqa) was evaluated in metastatic, castration sensitive, prostate cancer in combination with ADT and docetaxel versus ADT/docetaxel alone. This was not specifically in high-risk disease; however, the majority of subjects (>77%) had a Gleason score of 8 or greater – nearly 80% had bone metastases and all other subjects had visceral or non-regional lymph node metastases. The hazard ratio for death was 0.68 (95% CI, 0.57 – 0.80; p<0.001) with overall survival (OS) at four years reported as 62.7% in the darolutamide group compared to 50.4% in the placebo group, despite a high percentage of patients who received subsequent life-prolonging systemic therapies (primarily a different androgen-receptor pathway inhibitor) among those who entered the follow-up in the placebo group (374 of 495 patients (75.6%). The side effect profile of darolutamide (Nubeqa) was consistent with previous evaluation and a higher incidence of treatment related adverse events was higher during the period when patients received both docetaxel and darolutamide (Nubeqa), and progressively decreased thereafter.

Investigational or Not Medically Necessary Uses

I. Therapies in this policy are being evaluated in other conditions; however, quality data indicating safety and efficacy in the following settings are not yet available:
   A. Cushing's Syndrome
   B. Breast cancer
   C. Hepatocellular carcinoma
   D. Fallopian tube, ovarian, or uterine cancer

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Fizazi K, Shore N, Tammela TL, et al. Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2019;380(13):1235-1246.
2. National Comprehensive Cancer Network clinical practice guidelines, prostate cancer. Version 4.2023. Updated September 7, 2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
3. El-amm J, Aragon-ching JB. The Current Landscape of Treatment in Non-Metastatic Castration-Resistant Prostate Cancer. Clin Med Insights Oncol. 2019;13:1179554919833927.
4. Nubeqa [Package Insert]. 2022. Bayer HealthCare Pharmaceuticals Inc. Whippany, NJ.
5. Xtandi (enzalutamide) [prescribing information]. Northbrook, IL: Astellas Pharma US Inc; November 2023. Erleada [Prescribing Information]. 2019. Janssen Pharmaceuticals Companies. Horsham, PA.

6. Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. Ann Oncol. 2013;24(7):1802-7.
7. Loriot Y, Bianchini D, Ileana E, et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Ann Oncol. 2013;24(7):1807-12.
8. Bianchini D, Lorente D, Rodriguez-vida A, et al. Antitumour activity of enzalutamide (MDV3100) in patients with metastatic castration-resistant prostate cancer (CRPC) pre-treated with docetaxel and abiraterone. Eur J Cancer. 2014;50(1):78-84.
9. Smith MR, Saad F, Rathkopf DE, et al. Clinical Outcomes from Androgen Signaling-directed Therapy after Treatment with Abiraterone Acetate and Prednisone in Patients with Metastatic Castration-resistant Prostate Cancer: Post Hoc Analysis of COU-AA-302. Eur Urol. 2017;72(1):10-13.
10. Smith MR, Saad F, Chowdhury S, et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. N Engl J Med. 2018;378(15):1408-1418.
11. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2018;378(26):2465-2474.
12. Yonsa [Package Insert]. 2011. Sun Pharmaceuticals Industries, Inc. Canbury, NJ.
13. Chi KN., Agarwal N., Bjartell A., et al. Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med. 2019;381(1):13-24.
14. Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer. J Clin Oncol. 2019;37(32):2974-2986.
15. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. N Engl J Med. 2019;381(2):121-131.
16. Smith MR, Hussain M, Saad F, et al. Darolutamide and Survival in metastatic hormone-sensitive prostate cancer. N Engl Med 2022;386:1132-42.
17. Fizazi K, Foulon S, Carles J, et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design. Lancet. 2022 Apr 30;399(10336):1695-1707. doi: 10.1016/S0140-6736(22)00367-1. Epub 2022 Apr 8.
18. Attard G, Murphy L, Clarke NW, et al. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. Lancet. 2022;399(10323):447-460.
19. Zaorsky NG, Davis BJ, Nguyen PL, et al. The evolution of brachytherapy for prostate cancer. Nat Rev Urol. 2017;14(7):415-439.
20. Agarwal N, Azad AA, Carles J, et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial [published online ahead of print, 2023 Jun 2]. Lancet. 2023;S0140-6736(23)01055-3. doi:10.1016/S0140-6736(23)01055-3
21. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, et al. Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer. NEJM Evid. 2022;1(9). doi:10.1056/EVIDoa2200043
22. Freedland SJ, de Almeida Luz M, De Giorgi U, et al. Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer. N Engl J Med. 2023;389(16):1453-1465.

Related Policies

Policy Name	Disease state
olaparib (Lynparza)	Prostate cancer, metastatic castration-resistant, homologous recombination repair (HRR) gene-mutated
talazoparib (Talzenna)	Prostate cancer, metastatic castration-resistant, homologous recombination repair (HRR) gene-mutated

Policy Implementation/Update:

Action and Summary of Changes	Date
Added new indication for Xtandi (enzalutamide) in non-metastatic, castration sensitive prostate cancer upon FDA approval in November 2023. Xtandi was added to existing criteria. Updated step through Lynparza/abiraterone for mCRPC to delineate between patients with BRCAm vs HRRm.	02/2024

Addition of criteria for abiraterone off-label use in non-metastatic, castration sensitive prostate cancer given published meta-analysis, long-term overall survival data from the STAMPEDE trial, and updated NCCN prostate cancer guideline recommendation (category 2a). Addition of pathway to coverage for enzalutamide (Xtandi) in combination with talazoparib (Talzenna) for metastatic castration-resistant prostate cancer given new FDA approved indication. Addition of verbiage to address combination use of olaparib (Lynparza) with abiraterone for mCRPC. Added related policies table.	09/2023
Added 240 mg Erleada tablets to policy	02/2023
Addition of darolutamide (Nubeqa) for metastatic castration-sensitive prostate cancer given new FDA-approved indication; Addition of docetaxel in combination with abiraterone acetate for metastatic castration-sensitive prostate cancer with high volume metastatic burden based on category 1 NCCN recommendation; Changed name of policy to 'Second Generation Anti Androgen Agents'	10/2022
Require clinical rationale for use of generic abiraterone 500 mg instead of generic 250 mg	05/2022
Addition of Grade Group referenced with Gleason Score	05/2021
Additional of newly approved enzalutamide (Xtandi) 40 mg and 80 mg tablets	11/2020
Addition of enzalutamide (Xtandi) for castration sensitive prostate cancer given new FDA-approved indication. Removal of requirement upon renewal to change to generic abiraterone. Consolidation of requirements for agents in the setting of castration sensitive prostate cancer to streamline policy. Formatting updates	12/2019
Darolutamide (Nubeqa) new agent available, criteria converted to policy, and all agents combined into one policy. Requirement of generic abiraterone added unless contraindicated or not tolerated. Addition of use of GnRH therapy in metastatic castration sensitive disease included. Yonsa brand added. Erleada now FDA approved for castration sensitive disease.	08/2019
Generic abiraterone requirement added prior to use of branded 250 mg.	12/2018
Enzalutamide new indication of non-metastatic resistant prostate cancer added. Clinical notes added and appropriate routing through criteria.	08/2018
Apalutamide (Erleada) criteria created	04/2018
Abiraterone new indication of metastatic, high-risk castration sensitive prostate cancer added. LATITUDE trial information incorporated as well.	02/2018
Enzalutamide (Xtandi) criteria created	02/2013
Abiraterone (Zytiga) criteria created	09/2011

Policy Type: PA/SP Pharmacy Coverage Policy: UMP086

Split Fill Management*

Description

Selinexor (Xpovio) is an oral nuclear export inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
selinexor (Xpovio)	80 mg tablet twice weekly carton	Relapsed or refractory multiple myeloma (MM)	1 carton (32 tablets)/28 days
	100 mg tablet once weekly carton		1 carton (20 tablets)/28 days
	80 mg tablet once weekly carton		1 carton (16 tablets)/28 days
	60 mg tablet once weekly carton		1 carton (12 tablets)/28 days
	40 mg tablet once weekly carton		1 carton (8 tablets)/28 days
	60 mg tablet twice weekly carton	Relapsed or refractory diffuse large B-cell lymphoma (DLBCL)	1 carton (24 tablets)/28 days
	40 mg tablet twice weekly carton		1 carton (16 tablets)/28 days

Initial Evaluation

I. Selinexor (Xpovio) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a hematologist or oncologist; **AND**
   C. Not used in combination with any other oncology therapy unless outlined below; **AND**
   D. A diagnosis of **multiple myeloma** when **ONE** of the following are met:
      1. The provider attests to the following:
         i. The member has received ONE, but no more than THREE previous therapies; **AND**
            a. Previous treatments included at least one of the following medications:
               i. Bortezomib (Velcade)

ii. Carfilzomib (Kyprolis)
iii. Ixazomib (Ninlaro)
iv. Daratumumab (Darzalex)
v. Immunomodulatory agent (e.g., lenalidomide, pomalidomide); **AND**

b. Selinexor (Xpovio) will be used in combination with bortezomib (Velcade) AND dexamethasone; **OR**

ii. The member has received **FOUR** or more previous therapies; **AND**

a. Refractory to ALL of the following medications:
i. TWO proteasome inhibitors (e.g., bortezomib, carfilzomib)
ii. TWO immunomodulatory medications (e.g., lenalidomide, pomalidomide)
iii. An anti-CD38 monoclonal antibody (e.g., daratumumab); **AND**

b. Selinexor (Xpovio) will be used in combination with dexamethasone.

II. Selinexor (Xpovio) is considered investigational when used for all other conditions, including but not limited to:
A. Multiple myeloma when given as part of a quadruplet ("quad") regimen
B. Diffuse large B-cell lymphoma

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
I. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
II. Clinical documentation of response to treatment such as stabilization or improvement in disease or symptoms; **AND**
III. Provider attests to the following:
A. The member has received ONE, but no more than THREE previous therapies; **AND**
1. Selinexor (Xpovio) will be used in combination with bortezomib (Velcade) AND dexamethasone; **OR**
B. The member has received **FOUR** or more previous therapies; **AND**
1. Selinexor (Xpovio) will be used in combination with dexamethasone.

Supporting Evidence

I. As of February 2021, selinexor (Xpovio) has three FDA-approved indications:
- In combination with bortezomib and dexamethasone in adult patients with multiple myeloma who have received at least one prior therapy
- In combination with dexamethasone in adult patients with multiple myeloma who have previously received at least four prior therapies and whose disease is refractory to at

least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody (penta-refractory)

- Relapsed or refractory diffuse large B-cell lymphoma (DLBCL)

II. Multiple myeloma (MM)

- Selinexor (Xpovio) is indicated for use in two different multiple myeloma settings: (1) received at least one prior therapy (*BOSTON trial*) and (2) received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody *(STORM trial*).
- Selinexor (Xpovio) for treatment in the setting of penta-refractory MM was approved via the accelerated approval pathway, and continued approval was contingent upon verification and description of clinical benefit in confirmatory trials. Results from the BOSTON trial confirmed continued approval for use in the setting of penta-refractory MM.
    i. **STORM**: Phase 2, open-label trial of 79 patients in combination with dexamethasone only. No other oncolytic therapies were included in the drug regimen. Patients included were previously treated with glucocorticoids, an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 mAb **and** refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab.
        1. The primary endpoint was objective response rate (ORR), which occurred in 21%. Secondary outcomes included progression free survival (PFS) and overall survival (OS), which resulted in 2.3 and 9.3 months, respectively.
        2. The safety profile is as follows: Sixty percent of patients in the trial experienced grade 3-4 adverse events including thrombocytopenia, anemia, and neutropenia. Additionally, other serious adverse events occurred such as febrile neutropenia, serious infections, and fatal serious bleeding.
        3. Selinexor (Xpovio) has not been sufficiently studied in the penta-refractory setting with further clinical evaluation of safety and efficacy needed to confirm a net health benefit and place in therapy for this medication.
    ii. **BOSTON**: Phase 3, randomized, open-label trial of 402 patients in combination with bortezomib and dexamethasone (N= 195 SEL-BTZ-Dex) compared to a combination with bortezomib and dexamethasone only (N=207 BTZ-Dex). Patients included had received one to three previous different regimens for multiple myeloma. Patients who previously received proteasome inhibitors (mono- or combination therapy) were required to have had at least a partial response and at least a 6-month interval since their last proteasome inhibitor therapy, with no history of discontinuation of bortezomib due to Grade 3+ AEs.
        1. The primary efficacy endpoint was progression free survival (PFS), which was 13.93 months in the SEL-BTZ-Dex arm versus 9.46 months in the BTZ-Dex arm. Key secondary endpoints were overall survival (OS), which was not reached in the SEL-BTZ-Dex arm versus 25 months in the BTZ-Dex arm; overall response rate (ORR) of 76.4% in the SEL-BTZ-Dex arm versus 62.3% in the BTZ-Dex arm; duration of response (DoR) of 20.3 months in the SEL-BTZ-

Dex arm versus 12.9 months in the BTZ-Dex arm; time to response (TTR) of 1.1 months in the SEL-BTZ-Dex arm versus 1.4 months in the BTZ-Dex arm.

2. Safety results were analyzed in all patients who received at least one dose of the study drug (N=195 SEL-BTZ-Dex, N=204 BTZ-Dex). The most common adverse events (≥20% incidence) included thrombocytopenia, anemia, nausea, fatigue, decreased appetite, diarrhea, peripheral neuropathy, weight loss, asthenia, cataract, and vomiting. Selinexor (Xpovio) showed an 81% treatment discontinuation rate: 21% due to adverse events versus 16% in the BTZ-Dex arm.

- Recommended dosage for MM:
    i. In combination with bortezomib and dexamethasone is selinexor (Xpovio) 100 mg taken orally once weekly on Day 1 of each week until disease progression or unacceptable toxicity.
    ii. In combination with dexamethasone is selinexor (Xpovio) 80 mg taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity.
- As of February 2021, the National Comprehensive Cancer Network (NCCN) treatment guideline for previously treated multiple myeloma has included selinexor (Xpovio) in combination with bortezomib and dexamethasone as "Other Recommended Regimens" (Category 1 recommendation). Additionally, NCCN recommends selinexor (Xpovio) in combination with dexamethasone as "Useful in Certain Circumstances" for patients with relapsed/refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody (Category 2A recommendation).

III. Diffuse large B-cell lymphoma (DLBCL)

- **SADAL**: Phase 2, an open-label, single-arm, multi-cohort trial of 127 patients with de novo DLBCL or DLBCL transformed from previously diagnosed indolent lymphoma, previously treated with two to five lines of therapy and progressed after, or were not candidates for autologous stem-cell transplantation were included. Previous systemic regimens permitted included at least one course of anthracycline-based chemotherapy (unless contraindicated due to cardiac dysfunction, in which case, other active drugs such as etoposide, bendamustine, or gemcitabine were given) and at least one course of anti-CD20 immunotherapy such as rituximab. Low dose dexamethasone (4 mg) was permitted as it does not show anti-lymphoma activity. FDA approval was based on the overall response rate (ORR).
    i. The primary efficacy endpoint was overall response rate (ORR), which occurred in 28%, and the secondary endpoint was duration of response (DoR), which was 9.3 months. Based on analysis of this clinical trial data, quality of the evidence is considered low given the lack of comparator and open-label trial design, as well as, the lack of clinically meaningful outcomes in morbidity, mortality, and quality of life – medication efficacy has not yet been confirmed.

ii. Safety results were analyzed in all patients who received at least one dose of selinexor (Xpovio) (N=125). The most common adverse events (≥20% incidence) included thrombocytopenia, nausea, fatigue, anemia, decreased appetite, diarrhea, constipation, neutropenia, weight loss, vomiting, pyrexia, and asthenia. There are no specific contraindications to selinexor (Xpovio); however, warnings and precautions include: thrombocytopenia, neutropenia, gastrointestinal toxicity, hyponatremia, serious infection, neurological toxicity, and embryo-fetal toxicity. Selinexor (Xpovio) showed a 93% treatment discontinuation rate: 63% due to disease progression, 10% withdrawal by patient, 7% death, 6% physician decision, and 7% due to adverse events.

- Selinexor (Xpovio) for treatment in the setting of DLBCL received accelerated approval from the FDA based on ORR and DoR. Continued approval for this drug may be contingent upon verification of clinical benefit in confirmatory trials. There is a Phase 2/3 trial underway to assess rituximab + gemcitabine + dexamethasone + platinum (R-GDP) with or without selinexor (Xpovio) in patients with relapsed/refractory diffuse large B-cell lymphoma.
- Recommended dosage for DLBCL:
    i. Selinexor (Xpovio) 60 mg taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity.
- As of February 2021, the National Comprehensive Cancer Network (NCCN) treatment guideline for B-cell lymphomas has included selinexor (Xpovio) as third-line and subsequent treatment with a Category 2A recommendation.

Investigational or Not Medically Necessary Uses

I. Selinexor (Xpovio) has not been sufficiently studied for safety and efficacy for the conditions or settings listed below:
    A. Quadruple ("quad") regimen
        i. Although triplet regimens remain the standard of care for multiple myeloma, there is growing interest in quad regimens which may include the addition of monoclonal antibodies (e.g., daratumumab [Darzalex], elotuzumab [Empliciti]) to standard triplet backbone regimens. The current evidence available to support this use is limited to case series or small trials. Larger studies evaluating the safety and efficacy of these regimens are underway.
    B. Diffuse large B-cell lymphoma
        i. Refer to SADAL trial information under Supporting Evidence

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

Appendix

Table 1: Classification of Medications used for Multiple Myeloma

Proteasome Inhibitors	Immunomodulatory Agents	Monoclonal Antibodies	Histone Deacetylase Inhibitors	B-cell Maturation Antigen-Directed Antibody	Chemotherapy
• bortezomib • carfilzomib • ixazomib	• thalidomide • lenalidomide • pomalidomide	• elotuzumab • daratumumab • isatuximab-irfc	• panobinostat	• belantamab mafodotin-blmf	• cyclophosphamide • doxorubicin • cisplatin • etoposide • melphalan • bendamustine

Table 2: Selinexor (Xpovio) Dosage Reduction Steps for Adverse Reactions

	MM In combination with Bortezomib and Dexamethasone	MM In combination with Dexamethasone	DLBCL
Recommended Starting Dosage	100 mg once weekly	80 mg Days 1 and 3 of each week (160 mg total per week)	60 mg Days 1 and 3 of each week (120 mg total per week)
First Reduction	80 mg once weekly	100 mg once weekly	40 mg Days 1 and 3 of each week (80 mg total per week)
Second Reduction	60 mg once weekly	80 mg once weekly	60 mg once weekly
Third Reduction	40 mg once weekly	60 mg once weekly	40 mg once weekly
Fourth Reduction	Permanently discontinue	Permanently discontinue	Permanently discontinue

References

1. Xpovio [Prescribing Information]. Karyopharm therapeutics Inc. Newton, MA. Updated December 2020. Accessed February 2021.
2. National Comprehensive Cancer Network NCCN Guidelines: Multiple Myeloma 3.2019. June 2019. Available at https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed August, 2019.
3. Vogl DT, Dingli D, Cornell RF, et al. Selective Inhibition of Nuclear Export With Oral Selinexor for Treatment of Relapsed or Refractory Multiple Myeloma. J Clin Oncol. 2018;36(9):859-866.
4. IPD Analytics. Xpovio (selinexor) New Drug Approval. Published August 2019.
5. FDA Advisory Committee Meeting Introductory Comments. NDA 212306 selinexor. February 2019. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212306Orig1s000MultidisciplineR.pdf. Accessed August, 2019.
6. Mikhael J, Ismaila N, Cheung MC, et al. Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline. J Clin Oncol. 2019;37(14):1228-1263.
7. Kalakonda N, Maerevoet M, Cavallo F, et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial. *Lancet Haematol* 2020;7(7):e511-e522. Available at https://pubmed.ncbi.nlm.nih.gov/32589977/.
8. Grosicki S, Simonova M, Spicka I, et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. *Lancet* 2020;396:1563-73. Available at https://pubmed.ncbi.nlm.nih.gov/33189178/.
9. National Comprehensive Cancer Network NCCN Guidelines: Diffuse Large B-cell Lymphoma 1.2021. January 2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed February 2021.

10. National Comprehensive Cancer Network NCCN Guidelines: Multiple Myeloma 4.2021. December 2020. Available at https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed February 2021.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added split fill management, length of authorization. Updated quantity limits to include 40 mg tablet once weekly carton, as well as DLBCL dosage forms. Updated penta-refractory MM indication from E/I to allow criteria coverage. Added criteria coverage for new MM indication of at least one prior therapy. Added new DLBCL indication and quad-regimen for MM as E/I. Added additional supporting evidence to include more details surrounding all three indications. Added "Table 1: Classification of Medications used for Multiple Myeloma" and "Table 2: Selinexor (Xpovio) Dosage Reduction Steps for Adverse Reactions" under Appendix.	02/2021
Policy created	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP192

Split Fill Management*

Description

Selpercatinib (Retevmo) is an orally administered kinase inhibitor of RET.

Length of Authorization

- N/A

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
selpercatinib (Retevmo)	RET Fusion-Positive Non-Small Cell Lung Cancer RET-Mutant Medullary Thyroid Cancer RET Fusion-Positive Thyroid Cancer, in those that are radioactive iodine refractory RET Fusion-Positive Solid Tumors, locally advanced or metastatic	40 mg capsules	180 capsules/30 days
		40 mg tablets	
		80 mg capsules	120 capsules/30 days
		80 mg tablets	

Initial Evaluation

I. Selpercatinib (Retevmo) is considered investigational when used for all indications, including but not limited to Non-Small Cell Lung Cancer, Thyroid Cancer, and other locally advanced or metastatic solid tumors with RET-fusion.

Renewal Evaluation

I. N/A

Supporting Evidence

I. RET, a transmembrane receptor protein, is present at the surface of several tissue types. Alterations include fusions and point mutations – both are oncogenic drivers. Selpercatinib (Retevmo) is the first FDA-approved therapy that targets RET alterations specifically.

II. Selpercatinib (Retevmo) is a kinase inhibitor of RET. It is FDA-approved for adults with metastatic RET fusion-positive non-small-cell lung cancer (NSCLC), advanced or metastatic RET-mutant medullary thyroid cancer (MTC) in patients age 12 years and older, and advanced or metastatic RET fusion-positive thyroid cancer who are radioactive iodine (RAI)-refractory in patients age 12 years and older. As of September 2022, selpercatinib (Retevmo) also received

accelerated approval for the treatment of adult patients with locally advanced or metastatic solid tumors with a RET gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.

III. RET fusion-positive NSCLC, advanced or metastatic: First-line treatment options include cabozantinib (Cometriq®) or vandetanib (Caprelsa®) (not FDA-approved for lung cancer) or combinations of platinum-based chemotherapy, anti-PD-1/PD-L1 therapy, pemetrexed, and bevacizumab. In the second-line setting, additional options include various immunotherapy and chemotherapy treatments (e.g., taxanes, gemcitabine).

IV. RET-mutant MTC, advanced or metastatic: Systemic treatment may be warranted for high volume, symptomatic or progressive MTC. General treatment options include cabozantinib (Cometriq) or vandetanib (Caprelsa).

V. RET fusion-positive thyroid cancer: In persistent/recurrent or metastatic disease, radioactive iodine (RAI) is recommended. In those not amenable to RAI, general treatment options include lenvatinib (Lenvima®) or sorafenib (Nexavar®).

VI. **Clinical Trial in the setting of NSCLC, MTC, and Thyroid Cancer:**

- Selpercatinib (Retevmo) is being evaluated in one Phase 1/2, open-label, multi-cohort, single-arm trial in patients with RET abnormal, advanced solid tumors Interim results showed potential antitumor activity, based on objective response rate (ORR), in the three FDA-approved settings. Additional outcomes: progression-free survival (PFS) and overall survival (OS) at 12 months.
- RET fusion-positive NSCLC: Patients were advanced or metastatic, progressed on platinum-based chemotherapy or were systemic treatment naïve. Over half of pretreated patients also received anti-PD1/PD-L1 therapy (n=58).
- RET-mutant MTC: 98% had metastatic disease, and patients were previously treated with cabozantinib (Cometriq) and/or vandetanib (Caprelsa) or were treatment naïve to both. Ten patients were previously treated with platinum chemotherapy or anti-PD1/PD-L1 therapy.
- RET fusion-positive TC: Patients were not amenable to RAI therapy and may have been treated with lenvatinib (Lenvima) and/or sorafenib (Nexavar), or were naïve to both.

Clinical Efficacy in Pretreated Patients			
Outcome	**RET Fusion+ NSCLC (n=105)**	**RET-Mutant MTC (n=55)**	**RET Fusion-Positive TC (n=19)**
ORR (n)	67 (64%)	38 (69%)	15 (79%)
CR (n)	2 (2%)	5 (9%)	1 (5%)
PR (n)	65 (62%)	33 (60%)	14 (74%)
PFS (months)	16.5 (13.7-NE)	NE	20 (9.4-NE)
OS, 12 months (%)	88%	87%	NR
Clinical Efficacy in Treatment-Naïve Patients			
Outcome	**RET Fusion+ NSCLC (n=39)**	**RET-Mutant MTC (n=88)**	**RET Fusion-Positive TC (n=8)**
ORR (n)	33 (85%)	64 (73%)	8 (100%)
CR (n)	0	10 (11%)	1 (12.5%)
PR (n)	33 (85%)	54 (61%)	7 (87.5%)
PFS (months)	NE	23.6 (NE-NE)	NE

OS, 12 months (%)	NR	NR	NR

- For the treatment of RET-mutant medullary thyroid cancer and for RET-fusion positive thyroid cancer, selpercatinib (Retevmo) was FDA-approved under the accelerated approval pathway based on ORR. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials. This therapy is being evaluated in multiple other clinical Phase 2 and Phase 3 trials. The quality of the evidence is considered low at this time given the open-label trial design and lack of comparator arm. Given the observational data, medication efficacy remains uncertain. Additionally, the medication has an unfavorable safety profile.
- As of June 2020, safety data are based on a pooled population in 702 patients, 65% were exposed for six months or greater, and 34% were exposed for over one year. Ninety-five percent of patients received 160 mg twice daily.

VII. **Clinical Trial in the setting solid tumors with RET-fusion:**

- Selpercatinib (Retevmo) was FDA-approved under the accelerated approval pathway for the treatment of adult patients with locally advanced or metastatic solid tumors with a RET gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options. This indication and FDA approval is based on an ongoing phase 1/ 2 single-arm, open-label clinical trial (basket trial, LIBRETT001). Selpercatinib (Retevmo) was administered to a tumor agnostic cohort of 41 patients with solid tumors harboring RET fusions, which consisted of following tumor types: pancreatic cancer (12), colon (10), salivary gland (4), sarcoma (3), unknown primary (3), breast (2), skin carcinoma (2), cholangiocarcinoma (2), xanthogranuloma (2), and carcinoid, ovarian, pulmonary sarcoma, rectal neuroendocrine, and small intestinal tumors (1 patient each). Majority of these patients were pre-treated and progressed after one to two lines of systemic therapies.
- At a median duration of follow-up 18.8 months, selpercatinib (Retevmo) reported a 43.9% (28.5 – 60.3) objective response rate (ORR) across all tumor types, as measured by a blinded independent committee review. When measuring the duration of response and progression-free survival outcomes, more than half of the patients were censored due to being lost to follow up. Due to the lack of causality of ORR with long-term clinically meaningful outcomes of morbidity and mortality, the quality of the current data is considered low. It is unknown if selpercatinib (Retevmo) may provide true treatment benefit if and when tested in a larger comparator-controlled trial in the setting of solid tumors with RET fusions.
- Although the adverse reaction profile for selpercatinib (Retevmo) varied across participants with different tumor types, the basket trial did not provide significant safety signals other than those previously reported during the clinical trial in the setting of NSCLC and thyroid cancer.

VIII. Warnings and precautions: hepatotoxicity, hypertension, QT interval prolongation, hemorrhagic events, hypersensitivity, impaired wound healing, and embryo-fetal toxicity. There are no contraindications. Serious adverse reactions occurred in 33% of patients. The most frequent was pneumonia. Fatal adverse reactions occurred in 3% of individuals due to sepsis (n=1), cardiac arrest (n=3), respiratory failure (N=3).

IX. Common adverse reactions (≥25%): increase liver enzymes, laboratory abnormalities (≥25% each, glucose, leukocytes, albumin, calcium, creatinine, alkaline phosphatase, platelets, cholesterol, sodium), dry mouth, diarrhea, hypertension, fatigue, edema, rash, constipation. Permanent discontinuation due to adverse reactions occurred in 5%, dose interruptions in 42%, and dose reduction in 31% of patients.

X. Insight from oncology specialists indicate that the diagnosis of stage IV metastatic disease can include intra-pulmonary (disease contained within the lungs) and extra-pulmonary (disease spread to organs outside the lungs) metastases. Intra-pulmonary metastases are typically staged as M1a and described as one of the following situations: separate nodule in the other lung, pleural or pericardial nodules, or malignant pleural or pericardial effusions. The treatment approach for those with intra-pulmonary metastases should be individualized and include surgery and, when surgery is not feasible, standard systemic therapy.

XI. Targeted therapies in oncology have garnered interest in recent years and may be considered part of a paradigm shift in the management of solid tumors based on histology and actionable mutations. However, while initially effective, many targeted therapies have been associated with increased drug resistance after their initial use. Additionally, targeted therapy approach is also susceptible to failure due to acquired resistance and escape mutations.

XII. Ongoing research focuses on identifying potential novel biomarkers and mechanisms involved in resistance to these therapies. In this regard, conventional chemotherapy agents may remain practical and established therapeutic options for members, after progression on or after first-line therapies (e.g., platinum-based chemotherapy). Due to lack of conclusive clinical data to direct a path to curative therapies, NCCN guidelines for the treatment of majority of cancer types (e.g., NSCLC, cholangiocarcinoma, neuroendocrine, sarcoma) note that the best management for any patient with cancer is in a clinical trial setting, and participation in trial is especially encouraged. Patients participating in clinical trials receive regular care, often at leading health care facilities with experts in the field while participating in important medical research and further advancements in treatment, with close safety monitoring and follow-up. Participation in a clinical trial remains the most favorable treatment option for patients with advanced NSCLC. Despite the accelerated FDA-approval, and category 2A recommendations from NCCN, continued approval of selpercatinib (Retevmo) as a subsequent-line treatment of tumors harboring RET fusions, remains contingent upon verification of clinical benefit in confirmatory trials.

Investigational or Not Medically Necessary Uses

I. Selpercatinib (Retevmo) has not been sufficiently studied for safety and efficacy for any condition to date.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Retevmo [Prescribing Information]. Eli Lilly and Company. Indianapolis, IN. May 2020.
2. Adeniran AJ, Ahu Z, Gandhi M, et al. Correlation between genetic alterations and microscopic features, clinical manifestations, and prognostic characteristics of thyroid papillary carcinomas. Am J Surg Pathol. 2006. 30(2): 216-222.
3. Drilon A, Hu ZI, Lai GGY, Tan DSW. Targeting RET-driven cancers: lessons from evolving preclinical and clinical landscapes. Nat Rev Clin Oncol. 2018a Mar;15(3):151-67.
4. Guerra A, Sapio MR, Marotta V, Campanile E, Moretti MI, Deandrea M, et al. Prevalence of RET/PTC rearrangement in benign and malignant thyroid nodules and its clinical application. Endocr J. 2011;58(1):31-8.
5. Prasad ML, Vyas M, Horne MJ, Virk RK, Morotti R, Liu Z, et al. NTRK fusion oncogenes in pediatric papillary thyroid carcinoma in northeast United States. Cancer. 2016;122(7):1097-107.
6. Roy M, Chen H, Sippel RS. Current understanding and management of medullary thyroid cancer. Oncologist. 2013;18(10):1093-100.
7. Tappenden P, Carroll C, Hamilton J, Kaltenthaler E, Wong R, Wadsley J, et al. Cabozantinib and vandetanib for unresectable locally advanced or metastatic medullary thyroid cancer: a systematic review and economic model. Health Technol Assess. 2019 Feb;23(8):1-144.
8. Kato S, Subbiah V, Marchlik E, Elkin SK, Carter JL, Kurzrock R. RET aberrations in diverse cancers: next-generation sequencing of 4,871 patients. Clin Cancer Res. 2017 Apr;23(8):1988-97.
9. Sireci AN, Morosini D, Rothenberg S. Efficacy of immune checkpoint inhibition in RET fusion-positive non-small cell lung cancer patients (poster). Presented at the World Lung Cancer Conference; September 7-10, 2019. Barcelona, Spain. Available at: https://www.jto.org/article/S1556-0864(19)31499-6/fulltext. Accessed February 28, 2020.
10. National Comprehensive Cancer Network. Thyroid Carcinoma Clinical Practice Guidelines V1.2020. June 12, 2020. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx.
11. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer Treatment Guidelines V6.2020. June 15, 2020. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx.
12. Subbiah V, Wolf J, Konda B, et al. Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. Lancet Oncol. 2022 Oct;23(10):1261-1273.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
pralsetinib (Gavreto)	RET Fusion-Positive Non-Small Cell Lung Cancer
	RET-Mutant Medullary Thyroid Cancer
	RET Fusion-Positive Thyroid Cancer, in those that are radioactive iodine refractory

Policy Implementation/Update:

Action and Summary of Changes	Date
Added tablet variation to the QL table	04/2024
Reviewed expanded indication for Retevmo for the treatment of RET-fusion positive solid tumors; added relevant supporting evidence	03/2023
Added supporting evidence around stage IV metastatic disease and metastases.	10/2021
Policy created	08/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP193

Split Fill Management*

Description

Selumetinib (Koselugo) is a mitogen-activated protein kinase (MEK) inhibitor for both MEK 1 and 2 that inhibits the phosphorylation of extracellular signal related kinase (ERK) and reducing neurofibroma numbers, volume, and proliferation.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
selumetinib (Koselugo)	10 mg capsules	Neurofibromatosis type 1 (NF1)	120 capsules/30 days
	25 mg capsules		

Initial Evaluation

I. Selumetinib (Koselugo) may be considered medically necessary when the following criteria are met:
   A. Member is between two and 18 years of age; **AND**
   B. Medication is prescribed by, or in consultation with, a neurosurgeon or neurologist; **AND**
   C. Documentation of baseline comprehensive ophthalmic assessments; **AND**
   D. Documentation of baseline assessment of left ventricular ejection fraction (LVEF); **AND**
   E. Member has NOT experienced disease progression (increase in tumor size or tumor spread) while on a MEK inhibitor [e.g., binimetinib (Mektovi®), cobimetinib (Cotellic®), trametinib (Mekinist®)]; **AND**
   F. A diagnosis of **Neurofibromatosis type 1 (NF1)** when the following are met:
      1. Member has inoperable and symptomatic plexiform neurofibromas (PN); **AND**
      2. Symptoms affect quality of life (e.g. pain, impaired physical function, compression of vital organs, respiratory impairment, visual dysfunction, and neurological dysfunction); **AND**
      3. Diagnosis confirmed by genetic testing; **OR**
         i. Member meets at least one criterion:
            a. Six or more light brown spots (café-au-lait macule – CALMs) equal to, or greater than, 5 mm in longest diameter in prepubertal patients and 15 mm in longest diameter in post pubertal patient; **OR**

b. Freckling in the axillary or inguinal regions (Crowe sign); **OR**
c. Optic glioma (OPG); **OR**
d. Two or more iris hamartomas (Lisch nodules – dome-shaped gelatinous masses developing on the surface of the iris); **OR**
e. A distinctive osseous lesion, such as sphenoid wing dysplasia or long-bone dysplasia (with associated cortical thickening and medullary canal narrowing), with or without pseudoarthrosis; **OR**
f. A first-degree relative (parent, sibling, or child) with NF1.

II. Selumetinib (Koselugo) is considered investigational when used for all other conditions.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
IV. Member has **NOT** exhibited ophthalmic toxicity (e.g. blurred vision, photophobia, cataracts, or ocular hypertension) nor experienced a decrease of 10% or more below baseline in LVEF during treatment.

Supporting Evidence

I. The safety and efficacy of selumetinib (Koselugo) in pediatric patients two years of age or older with NF1 who have inoperable PN was established in the SPRINT trial (a phase II, open-label, single arm, multicenter clinical trial).
II. Patients older than 18 years of age are being studied in a phase 2, open label, single site clinical trial, with the primary outcome being to determine an objective response rate. The study is still ongoing and therefore has no published safety and efficacy data to support the use in adult patients (those 18 years of age or older).
III. NF1 is a multifaceted disease state and selumetinib (Koselugo) has a complex dosing regimen and safety profile; therefore, it should be prescribed by, or in consultation with, a specialist in the treatment and management of NF1.
IV. Cardiomyopathy, defined as a decrease in left ventricular ejection fraction (LVEF) of 10% or more below baseline, occurred in 23% of the 74 pediatric patients who received selumetinib (Koselugo) in the clinical trial. The safety and efficacy, of use in those with a history of impaired LVEF or a baseline ejection fraction that is below the institutional LLN, has not been established.
V. Blurred vision, photophobia, cataracts, and ocular hypertension occurred in 15% of 74 pediatric patients receiving selumetinib (Koselugo). Blurred vision resulted in dose interruption in 2.7% of patients. Ocular toxicity resolved in 82% of 11 patients. Comprehensive ophthalmic assessments

prior to initiating, and at regular intervals during treatment, for new or worsening visual changes is recommended.

VI. There is no published data from a head-to-head study between selumetinib (Koselugo) and other MEK inhibitors [e.g., binimetinib (Mektovi®), cobimetinib (Cotellic®), trametinib (Mekinist®)] to show effectiveness for the treatment of pediatric patients two years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).
There is no data to show one MEK inhibitor could overcome common mechanisms of resistance of MEK inhibitors.

VII. The safety and efficacy of selumetinib (Koselugo) was evaluated in patients with NF1 who have inoperable (defined as a PN that could not be completely removed without risk for substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness, or high vascularity of the PN) and symptomatic [defined as PNs that may located around the orbit, face, upper and lower limbs, back, thorax, abdomen, neck brachial plexus and/or lumbosacral plexus, which result in clinical symptoms such as disfigurement, motor dysfunction (weakness and restricted range of motion), pain, respiratory impairment, visual dysfunction, and neurological dysfunction] PNs.

VIII. Per the American Academy of Pediatrics, National Institutes of Health (NIH) consensus development conference regarding NF1, to establish a diagnosis of NF1, two out of seven criteria have to have been met: **1.** Six or more light brown spots on skin (café-au-lait macule – CALMs) equal to, or greater than, 5 mm in longest diameter in prepubertal patients and 15 mm in longest diameter in post pubertal patient. **2.** Two or more neurofibromas of any type or 1 plexiform neurofibroma. **3.** Freckling in the axillary or inguinal regions (Crowe sign). **4.** Optic glioma (OPG). **5**. Two or more iris hamartomas (Lisch nodules – dome-shaped gelatinous masses developing on the surface of the iris). **6**. A distinctive osseous lesion, such as sphenoid wing dysplasia (partial or complete absence of the greater wing of the sphenoid) or long-bone dysplasia (with associated cortical thickening and medullary canal narrowing), with or without pseudoarthrosis (unsuccessful spinal fusion). **7.** A first-degree relative (parent, sibling, or child) with NF1

    A. NF1 genetic testing may be performed for purposes of diagnosis, but if a child fulfills diagnostic criteria for NF1, molecular genetic confirmation is usually unnecessary. Molecular diagnosis of NF1 is available based on DNA analysis for a pathogenic variant in the NF1 gene. Only 4 genotype-phenotype correlations have been established (deletion of the entire NF1 gene, specific 3-base deletion in exon 22, Amino acid substitution at codon 1809, some missense or splicing variants are associated with “spinal NF1,”).

Investigational or Not Medically Necessary Uses

I. Selumetinib (Koselugo) has not been FDA-approved, or sufficiently studied for safety and efficacy for other conditions except neurofibromatosis type 1 (NF1) with inoperable PNs.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Koselugo [Prescribing Information]. AstraZeneca Pharmaceuticals LP: Wilmington, DE. April 2020.
2. David T. Miller, MD, PhD, FAAP, Debra Freedenberg, MD, PhD, FAAP, Elizabeth Schorry, MD, et al. American Academy of Pediatrics (AAP) COUNCIL ON GENETICS, AAP AMERICAN COLLEGE OF MEDICAL GENETICS AND GENOMICS. Health Supervision for Children with Neurofibromatosis Type 1. Pediatrics. May 2019. 143(5). e20190660
3. Andrea M. Gross, M.D., Pamela L. Wolters, Ph.D., Eva Dombi, M.D., et al. Selumetinib in Children with Inoperable Plexiform Neurofibromas. N Engl J Med 2020; 382:1430-1442.
4. National Cancer Institute (NCI). MEK 1/2 Inhibitor Selumetinib (AZD6244 Hydrogen Sulfate) in Adults With Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas. ClinicalTrials.gov NCT02407405
5. Ly KI, Blakeley JO. The Diagnosis and Management of Neurofibromatosis Type 1. Med Clin North Am. Nov 2019; 103(6):1035-1054
6. Boyd, K. P., Korf, B. R., & Theos, A. Neurofibromatosis type 1. Journal of the American Academy of Dermatology. 2009. 61(1), 1–16

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	08/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP031

Description
Granulocyte-colony stimulating factors (G-CSF) and granulocyte macrophage-CSF (GM-CSF) act on the hematopoietic cells by binding to specific cell surface receptors thereby stimulating the production, maturation, and activation of neutrophils.

Length of Authorization
- Initial: Four months
- Renewal: Four months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
Neupogen (filgrastim)	• Bone marrow transplant • Peripheral progenitor cell (PBPC) mobilization and transplant • Prophylactic use in patients with non-myeloid malignancy • Treatment of chemotherapy-induced febrile neutropenia • Neutropenic complications from prior chemotherapy cycle • Acute myeloid leukemia (AML) patient following induction or consolidation chemotherapy • Bone marrow transplantation failure or engraftment delay • Severe chronic neutropenia • Myelodysplastic syndrome • Exposure to myelosuppressive doses of radiation	300 mcg/mL vial	15 prefilled syringes or vials per 30-day supply
		300 mcg/0.5mL syringe	
		480 mcg/1.6mL vial	
		480 mcg/0.8mL syringe	
Zarxio (filgrastim-sndz)*		300 mcg/0.5mL syringe	
		480 mcg/0.8mL syringe	
Nivestym (filgrastim-aafi)		300 mcg/mL vial	
		300 mcg/0.5mL syringe	
		480 mcg/1.6mL vial	
		480 mcg/0.8mL syringe	
Granix (tbo-filgrastim)		300 mcg/mL vial	
		300 mcg/0.5mL syringe	
		480 mcg/1.6mL vial	
		480 mcg/0.8mL syringe	
Releuko (filgrastim-ayow)		300 mcg/mL vial	
		300 mcg/0.5mL syringe	
		480 mcg/1.6mL vial	
		480 mcg/0.8mL syringe	
Leukine (sargramostim)		250 mcg/mL vial	

Initial Evaluation

I. Products may be considered medically necessary when the following criteria below are met:

Zarxio is the preferred short-acting G-CSF
- **Patients must have failed, or have a contraindication, or intolerance to Zarxio prior to consideration of any other short-acting G-CSF**
  - There is no prior authorization* required for Zarxio unless requesting above the quantity limit noted above.

A. A diagnosis of:
    1. **Peripheral Blood Progenitor Cell (PBPC) mobilization and transplant; OR**
    2. **Patient who experienced a neutropenic complication from a prior cycle of the same chemotherapy; OR**
    3. **Bone Marrow Transplant (BMT); OR**
    4. **Bone Marrow Transplantation (BMT) failure or Engraftment Delay; OR**
    5. **Patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome); OR**
    6. **Acute Myeloid Leukemia (AML) patient following induction or consolidation chemotherapy; OR**
    7. **Prophylactic use in patients with non-myeloid malignancy; AND**
        i. Member is undergoing myelosuppressive chemotherapy with an expected incidence of febrile neutropenia of 20% or greater; **OR**
        ii. Member is undergoing myelosuppressive chemotherapy with an expected incidence of febrile neutropenia of 10% or greater **AND** has one or more of the following co-morbidities:
            a. Age 65 years or older AND receiving full dose intensity chemotherapy
            b. History of recurrent febrile neutropenia from chemotherapy
            c. Extensive prior exposure to chemotherapy
            d. Previous exposure of pelvis, or other areas of large amounts of bone marrow, to radiation
            e. Pre-existing neutropenia (ANC ≤ 1000/mm3) or bone marrow involvement with tumor
            f. Member has a condition that can potentially increase the risk of serious infection (i.e. HIV/AIDS)
            g. Infection/open wounds
            h. Recent surgery
            i. Poor performance status
            j. Poor renal function (creatinine clearance <50)
            k. Liver dysfunction (elevated bilirubin >2.0)
            l. Chronic immunosuppression in the post-transplant setting including organ transplant; **OR**
    8. **Myelodysplastic Syndrome**; **AND**
        i. Endogenous serum erythropoietin level of ≤500 mUnits/mL; **AND**
        ii. Member has lower risk disease (i.e., defined as IPSS-R [Very Low, Low, Intermediate], IPSS [Low/Intermediate-1], WPSS [Very Low, Low, Intermediate]); **AND**
        iii. Used for treatment of symptomatic anemia in patients without del(5q); **AND**
        iv. Member is receiving concurrent therapy with Erythropoiesis Stimulating Agents (ESA); **AND**
            a. Member has ring sideroblasts < 15% and will use in combination with lenalidomide following no response (despite adequate iron stores) or loss or response to an ESA alone; **OR**

b. Member has ring sideroblasts ≥ 15%; **OR**

9. **Treatment of chemotherapy-induced febrile neutropenia; AND**
    i. Member has been on prophylactic therapy with filgrastim; **OR**
    ii. Member has not received prophylactic therapy with a granulocyte colony stimulating factor; **AND**
        a. Member has one or more of the following risk factors for developing infection-related complications:
            i. Sepsis Syndrome
            ii. Age >65
            iii. Absolute neutrophil count [ANC] <100/mcL
            iv. Duration of neutropenia expected to be greater than 10 days
            v. Pneumonia or other clinically documented infections
            vi. Invasive fungal infection
            vii. Hospitalization at the time of fever
            viii. Prior episode of febrile neutropenia; **OR**
10. **Severe chronic neutropenia; AND**
    i. Member has an absolute neutrophil count (ANC) < 500/mm3; **AND**
    ii. Member has a diagnosis of one of the following:
        a. Congenital neutropenia
        b. Cyclic neutropenia
        c. Idiopathic neutropenia; **OR**
11. **Management of CAR-T related Toxicity; AND**
    i. Member has been receiving therapy with CAR T-cell therapy (e.g. tisangenleclecleucel (Kymriah), Axicabtagene Ciloleucel (Yescarta), etc.); **AND**
    ii. Member is experiencing neutropenia related to their therapy.

Renewal Evaluation

I. Same as initial prior authorization policy criteria.

Supporting Evidence

I. Indications listed under section I are supported by FDA-labeled indication(s) or are recommended per Compendia.

II. Quantity limits are based on usual FDA dosing of once daily until complete blood count (CBC) or absolute neutrophil count (ANC) has returned to an appropriate range. Generally, chemotherapy is administered every 2-3 weeks, whereby frequency of filgrastim is not expected to be needed for greater than two weeks. For other indications, such as transplant, myelodysplastic syndrome, or chronic neutropenia, therapy is continued until adequate neutrophil recovery is achieved. Accordingly, quantity exceptions may be considered when frequent administration of filgrastim is deemed medically necessary.

III. Duration of approval is based on usual duration of chemotherapy or radiation therapy cycle. There is no guideline consensus on optimal duration of G-CSF or GM-CSF treatment or prophylaxis, therefore continued use is driven by clinical scenario and lab monitoring.

IV. Risk of developing febrile neutropenia is related to intensity and toxicity of chemotherapy regimen, as well as patient-specific factors. Expected incidence of febrile neutropenia percentages for myelosuppressive chemotherapy regimens can be found in the NCCN Hematopoietic Growth Factors Clinical Practice Guideline at NCCN.org. NCCN and ASCO guidelines recommend use of a G-CSF for prophylaxis when risk is 20% or greater. When risk is between 10-20%, prophylactic G-CSF is recommended when patients have one or more of the risk factors listed above. Routine prophylaxis with G-CSF for febrile neutropenia when risk is less than 10% is not recommended.

V. In myelodysplastic syndromes (MDS), G-CSF may be used in combination with an erythropoiesis-stimulating agent (ESA) when patients have symptomatic anemia, as G-CSF can boost erythroid response. Likelihood of erythroid response is influenced by serum erythropoietin, MDS prognostic category, presence of ring sideroblasts, and other factors, therefore criteria outlined above follow NCCN guidelines to target the patient population expected to achieve a response.

VI. All FDA-approved biosimilars undergo a rigorous testing process to compare safety, purity, and potency between the proposed biosimilar and the parent or originator product, otherwise known as the reference product, to ensure there are no clinically meaningful differences. Only minor differences between products are allowed, such as in clinically inactive components. Biosimilars may be approved for all, or a subset, of the indications for the reference product. It is not uncommon for biosimilars to have fewer labeled indications if the reference product has remaining patent or exclusivity rights. It can be expected that biosimilar products will have the same clinical efficacy and safety profile as the reference product due to thorough FDA testing. With a goal to increase access to high-quality, cost-effective care, biosimilars may fill an unmet need as a more affordable alternative to brand biologic therapies. Notably, NCCN Guidelines similarly recommend that FDA-approved biosimilars be used as substitutes for originator filgrastim and pegfilgrastim. In addition, ASCO recommends that pegfilgrastim, filgrastim and biosimilars be considered therapeutically equivalent, with product selection being based on convenience, cost and clinical situation (i.e., chemotherapy frequency). As such, trial of preferred short-acting G-CSF biosimilar Zarxio (filgrastim-sndz) is required prior to approval of non-preferred filgrastim products.

References

1. Neupogen [Prescribing Information]. Amgen Inc. Thousand Oaks, CA. February 2021.
2. Zarxio [Prescribing Information]. Sandoz Inc. Princeton, NJ. August 2019.
3. Nivestym [Prescribing Information]. Hospira Inc., a Pfizer Company. Lake Forest, IL. July 2018.
4. Granix [Prescribing Information]. UAB Teva Baltics. Vilnius, Lithuania. November 2019.
5. Leukine [Prescribing Information]. Sanofi-aventis U.S. LLC. Bridgewater, NJ. March 2018.
6. Releuko [Prescribing Information]. Kashiv BioSciences, LLC. Piscataway, NJ. February 2022.
7. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of wbc growth factors: American Society of Clinical Oncology clinical practice guideline update. JCO. 2015;33(28):3199-3212.
8. Wisconsin Physicians Service Insurance Corporation. Local Coverage Determination (LCD): Human Granulocyte/Macrophage Colony Stimulating Factors (L34699). Centers for Medicare & Medicaid Services, Inc. Updated on 1/23/2018 with effective date 02/1/2018. Accessed March 2018.

9. First Coast Service Options, Inc. Local Coverage Determination (LCD): G-CSF (Neupogen®, Granix™, Zarxio™) (L34002). Centers for Medicare & Medicaid Services, Inc. Updated on 6/10/2016 with effective date 7/5/2016. Accessed March 2018.
10. National Government Services, Inc. Local Coverage Article: Filgrastim, Pegfilgrastim, Tbofilgrastim, Filgrastim-sndz (e.g., Neupogen®, Neulasta™, Granix™, Zarxio™) - Related to LCD L33394 (A52408). Centers for Medicare & Medicaid Services, Inc. Updated on 9/23/2016 with effective date 10/1/2016. Accessed March 2018.
11. Palmetto GBA. Local Coverage Determination: White Cell Colony Stimulating Factors (L37176). Centers for Medicare & Medicaid Services, Inc. Updated on 12/7/2017 with effective date 2/26/2018. Accessed March 2018.
12. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology for Hematopoietic Growth Factors, Version 1.2022. Updated December 22, 2021.
13. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Myelodysplastic Syndromes, Version 3.2022. Updated January 13, 2022.
14. U.S. Food and Drug Administration. Biosimilars – Healthcare provider materials. Updated July 28, 2021. https://www.fda.gov/drugs/biosimilars/health-care-provider-materials?utm_campaign=cder-factsheets&utm_content=&utm_medium=social&utm_source=linkedin
15. Biologics and Biosimilars Collective Intelligence Consortium. Biosimilar facts. https://www.bbcic.org/resources/biosimilars-facts.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
Long-acting Granulocyte Colony Stimulating Factor (G-CSF)	Prophylactic use in patients with non-myeloid malignancy
	Neutropenic complications from prior chemotherapy cycle
	Exposure to myelosuppressive doses of radiation
	Bone marrow transplantation failure or engraftment delay
	Peripheral progenitor cell (PBPC) mobilization and transplant

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated policy supporting evidence and references. Added related policies table.	08/2022
Added Releuko (filgrastim-ayow) to policy in the non-preferred position	04/2022
Updated quantity level limit to allow 15 doses per 30-day supply	12/2019
Policy title change, designate Zarxio as a preferred product, add “No PA Required” to Initial Evaluation Section 1 boxed information	10/2019
Previous Reviews	12/2018
Added Nivestym, biosimilar to Neupogen	10/2018
Previous Reviews	02/2018; 07/2018
Criteria update. Zarxio is the preferred short-acting G-CSF	2/2017

Policy Type: PA Pharmacy Coverage Policy: UMP106

Description

Simvastatin (Zocor) is an orally administered 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor used to reduce LDL-C and prevent cardiovascular events.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
Simvastatin (Zocor)	80 mg tablets	Prevention of cardiovascular events/cardiovascular disease and reduce the risk of atherosclerotic cardiovascular disease, homozygous familial hypercholesterolemia	30 tablets/30 days

Initial Evaluation

I. **Simvastatin 80 mg (Zocor)** may be considered medically necessary when the following criteria below are met:
   A. Member has been established and stabilized on the 80 mg dose for a duration of 12 or more months without evidence of muscle toxicity (e.g. myopathy, rhabdomyolysis) within the past 12 months.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent; **AND**
II. Member has exhibited improvement or stability of disease symptoms; **AND**
III. Member has not experienced symptoms of muscle toxicity (e.g. myopathy, rhabdomyolysis).

Supporting Evidence

I. In 2011, the FDA issued a dose limitation on simvastatin 80 mg stating that it should not be started in new patients and should only be used in patients who have been taking this dose for 12 months or more without evidence of muscle injury (myopathy). Furthermore, 2018 AHA/ACC guidelines note simvastatin 80 mg/day is not recommended due to increased risk of myopathy. If patient is unable to achieve LDL-C goal with simvastatin 40 mg/day, switch to a high-intensity statin.

II. The SEARCH trial was a seven-year, randomized, double-blind study that compared the efficacy and safety of simvastatin 80 mg versus simvastatin 20 mg, with or without vitamin B12 and folate in survivors of myocardial infarction.
    - Incidence of major vascular events between the simvastatin 80 mg group and simvastatin 20 mg group was 24.5% vs 25.7%, respectively (95% CI 0.88, 1.01, p=0.10).
    - 0.9% of patients in the simvastatin 80 mg group experienced myopathy versus 0.02% in the simvastatin 20 mg group. Risk for myopathy and rhabdomyolysis was highest in the first 12 months of therapy.

References

1. Zocor [Prescribing Information]. Whitehouse Station, NJ: Merck & Co., Inc. 1991.
2. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. *Lanciet*. 2010;376(9753):1658-1669.
3. U.S. Food & Drug Administration. (2011). FDA Drug Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury. Retrieved from https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-new-restrictions-contraindications-and-dose-limitations-zocor.
4. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139(25):e1082-e1143. doi:10.1161/CIR.0000000000000625[PubMed 30586774]

Policy Implementation/Update:

Action and Summary of Changes	Date
Updates to wording of initial criteria in efforts to clarify policy intent	05/2021
Criteria transitioned to policy with supporting evidence section added.	10/2019
New criteria	01/2017

Policy Type: PA/SP Pharmacy Coverage Policy: UMP259

Description

Sirolimus (Hyftor) is a topically administered mammalian target of rapamycin (mTOR) inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
sirolimus (Hyftor)	Facial angiofibroma associated with Tuberous Sclerosis	0.2% topical gel	6-11 years of age: 20 grams/30 days
			12 years of age and older: 30 grams/30 days

Initial Evaluation

I. **Sirolimus (Hyftor)** may be considered medically necessary when the following criteria are met:
   A. Member is 6 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a dermatologist or neurologist; **AND**
   C. Provider attestation that the member has facial angiofibroma, associated with tuberous sclerosis confirmed by genetic testing and/or clinical symptoms; **AND**
   D. Provider attestation that facial angiofibroma is associated with one or more of the following: bleeding, intense itching, pain, change in physical appearance, recent enlargement, or recent increase in number of lesions; **AND**
   E. Treatment with topical compounded sirolimus (gel, cream, or ointment) has been ineffective, contraindicated, or not tolerated; **AND**
   F. Previous treatment with surgery (shave excision, cryotherapy, electrodessication, radiofrequency ablation, dermabrasion) has been ineffective, contraindicated, or not tolerated; **OR**
      1. Previous treatment with laser therapy (ablative laser resurfacing, pulse dye laser) has been ineffective, contraindicated, or not tolerated.

II. Sirolimus (Hyftor) is considered investigational when used for all other conditions, including but not limited to:
   A. Tufted angiomas
   B. Fibroma or angiofibroma not associated with tuberous sclerosis complex
   C. Non FDA-approved dermatologic conditions

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Documentation that member has exhibited improvement or stability in extent and/or severity of angiofibroma (e.g., reduction in angiofibroma size and redness).

Supporting Evidence

I. Tuberous sclerosis complex (TSC) is a rare genetic multisystem disorder associated with the formation of benign tumors in various organ systems throughout the body, most commonly including the skin, brain, eyes, heart, kidneys, and lungs. Skin manifestations of TSC occur in up to 95% of individuals and include facial angiofibromas, hypomelanotic macules, fibrous plaques, Shagreen patches, and ungual fibromas. Most patients with TSC present with angiofibromas with onset commonly occurring in early childhood or early adulthood. Angiofibromas are benign reddish pink bumps located on the face, and without treatment they can cause facial disfigurement, bleeding, itching, erythema, and significant psychosocial consequences.
II. Per the International Tuberous Sclerosis Complex Diagnostic Criteria Surveillance and Management Recommendations, the diagnosis of tuberous sclerosis should be confirmed by genetic testing through identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue. In the absence of TSC mutations, diagnosis can be made through identification of clinical features including but not limited to fibrous cephalic plaque, hypomelanotic macules, ungual fibromas, Shagreen patch, multiple retinal hamartomas, cortical dysplasia, subependymal nodules, subependymal giant cell astrocytoma's, cardiac rhabdomyoma, lyphangiolelomyomatosis, and angiomyolipomas.
III. While there are limited treatment options for this condition, the International Tuberous Sclerosis Complex Diagnostic Criteria Surveillance and Management Recommendations recommend the use of topical compounded sirolimus (category 1 recommendation, based on a high-level of evidence and uniform consensus). Studies have evaluated compounded formulations ranging from 0.1% to 1% in a variety of vehicles. Smaller and flatter appearing lesions tend to respond better to topical sirolimus, so early treatment is recommended. Sirolimus (Hyftor) has not been evaluated against compounded sirolimus for the treatment of TSC angiofibroma, therefore comparative efficacy and safety remain uncertain. However, the chemical entity in both products is the same, therefore they are expected to provide similar safety and efficacy, even in the absence of a commercially available, FDA-labeled indication for compounded sirolimus. Further, given the long-established safety, efficacy, and cost effectiveness of compounded sirolimus, trial is required prior to use of sirolimus (Hyftor).
IV. Guidelines recommend surgical approaches (category 2B, based on lower-level evidence and consensus that the intervention is appropriate) for angiofibromas rapidly changing in size and/or number, causing pain, bleeding, irritation, disfigurement, or impaired function. These procedures include shave excision, cryotherapy, electrodessication, radiofrequency ablation,

dermabrasion, and laser therapy. They have been standardly used for angiofibroma management, though patients may not be candidates for surgery depending on anesthetic risk, age, active infection, uncontrolled diabetes, pregnancy, etc. Contraindications for laser therapy may include malignant carcinoma, irradiation of neck, epilepsy, exposure of retina, cognitive impairment, and pregnancy. Specifically, younger children may benefit from pulsed-dye laser therapy and adolescence ablative laser therapy to reduce facial erythema.

V. The FDA-approval of sirolimus (Hyftor) was based off a phase 3, 12-week, multicenter, randomized, double-blind, placebo-controlled trial. The study population included 62 adults and pediatric patients greater than 6 years of age, with a definitive diagnosis of TSC, 3 or more reddish papules of facial angiofibromas (> 2 mm diameter), and a past difficulty with or did not want laser or surgical therapy. The concurrent use of any mTOR inhibitor, topical tacrolimus, topical steroids, topical antibiotics, topical vitamin D, adapalene, benzyl peroxide, ibuprofen piconol, resorcinol, and zinc-salicylic acid, were prohibited. Population characteristics were as follows: mean age 22 years (range of 6-53 years), 42% of patients had intellectual impairment, 60% had epilepsy,28% had prior mTOR use (including topical sirolimus), and 32% had prior laser therapy, surgical resection, or liquid nitrogen therapy. The primary endpoint was composite improvement of angiofibroma size and color at week 12, which was met with 5 (17%) improved and 13 (43%) markedly improved in the sirolimus group compared to zero participants in the placebo group, with 84% rated unchanged. The secondary endpoints were response rates for composite, size, color, and plaques, and change in Dermatology Life Quality Index (DLQI) and Children's DLQI (CDQLI). The response rates for size, color, and plaques were statistically significant while the change from baseline in DLQI and CDLQI was not. The most common adverse events included dry skin (40%), application site irritation (37%), and itching (17%). Overall, this was a well-designed phase 3 clinical trial that showed statistical improvement in composite response rate and individual size, color and plaque response rates, however clinical meaningfulness of these endpoints and measurement tool remain unknown. Applicability to the larger TSC population is limited due to a large proportion of the population having previously been treated with surgery, laser or mTOR inhibitor therapy.

VI. The initial authorization length of three months is supported by clinical study duration of 12 weeks and prescribing information guidance which indicates that if symptoms do not improve by week 12 of treatment, prescriber should reevaluate the need for continuation of the medication.

VII. Quantity limits are based on the maximum daily doses used in pivotal study and as indicated by the FDA, and are expected to be sufficient, even if a large majority of the face is impacted. If symptoms do not improve within 12 weeks of consistent use and excessive quantities are needed, alternative treatment strategies that have the potential to be more efficacious and cost effective should be considered.

References

1. Hyftor [Prescribing Information]. Bethesda, MD: Noblepharma. February 2022.
2. Macri A, Kwan E, Tanner LS. Cutaneous angiofibroma. In: StatPearls. StatPearls Publishing; 2022.
3. Northrup H, Aronow ME, Bebin EM, et al. Updated international tuberous sclerosis complex diagnostic criteria and surveillance and management recommendations. Pediatric Neurology. 2021;123:50-66.

4. Wataya-Kaneda M, Ohno Y, Fujita Y, et al. Sirolimus gel treatment vs placebo for facial angiofibromas in patients with tuberous sclerosis complex: a randomized clinical trial. JAMA Dermatol. 2018;154(7):781.
5. UpToDate. Tuberous sclerosis complex: Genetics, clinical features, and diagnosis. Updated April 6, 2022. Accessed May 5, 2022.
6. UpToDate. Tuberous sclerosis complex: Management and prognosis. Updated April 6, 2022. Accessed May 5, 2022
7. Navratil L, Kymplova J. Contraindications in noninvasive laser therapy: truth and fiction. Journal of Clinical Laser Medicine & Surgery. 2002;20(6):341-343.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
everolimus (Afinitor®, Afinitor Disperz®)	Partial seizure, adjunct, tuberous sclerosis syndrome
	Angiomyolipoma of the kidney, tuberous sclerosis syndrome
	Breast cancer, advanced, HR+, HER2 -, in combination with exemestane after failure with letrozole or anastrozole
	Subependymal giant cell astrocytoma
	Renal cell carcinoma, advanced disease
	Neuroendocrine tumor, gastrointestinal, lung or pancreatic, unresectable locally advanced or metastatic
cannabidiol (Epidiolex®)	Tuberous Sclerosis Complex
	Lennox-Gastaut Syndrome
	Dravet Syndrome

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	07/2022

Policy Type: PA/SP Pharmacy Coverage Policy: UMP186

Description

Sodium oxybate (Xyrem, Lumryz) and calcium, magnesium, potassium, sodium oxybates (Xywav) are orally administered metabolites of the neurotransmitter GABA that act as central nervous system depressants with an unknown mechanism of action.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
generic sodium oxybate sodium oxybate (Xyrem) calcium, magnesium, potassium, sodium oxybates (Xywav)	Narcolepsy with cataplexy or excessive daytime sleepiness in patients greater than 7 years of age Idiopathic hypersomnia in adults	500 mg/mL	540 mL/30 days
sodium oxybate oral powder for suspension (Lumryz)	Narcolepsy with cataplexy or excessive daytime sleepiness in adult patients Idiopathic hypersomnia in adults	4.5g packet 6g packet 7.5g packet 9g packet	270 grams/30 days

Initial Evaluation

I. **Generic sodium oxybate, sodium oxybate (Xyrem), sodium oxybate ER (Lumryz), or calcium, magnesium, potassium, sodium oxybate (Xywav)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, a sleep specialist, psychiatrist, or neurologist; **AND**
   B. Medication will not be used in combination with sedative hypnotic agents (e.g. benzodiazepines, barbiturates, zolpidem tartrate); **AND**
   C. Provider attestation the member does not have a succinic semialdehyde dehydrogenase deficiency; **AND**
   D. Provider attestation the member does not have a history of substance abuse; **AND**
   E. If the request is for brand Xyrem: documentation of intolerance or contraindication to generic sodium oxybate; **AND**

F. A diagnosis of one of the following:
    1. **Narcolepsy with cataplexy**; **AND**
        i. Member is seven years of age or older; **OR**
            a. If the request is for sodium oxybate ER (Lumryz), member is 18 years of age or older; **AND**
        ii. Confirmation of cataplexy defined as episodes of sudden loss of muscle tone; **AND**
        iii. Symptoms have been present for at least three months; **AND**
        iv. Documented impairment/limitation of activities of daily living (e.g., missing school/work, household chores, driving); **AND**
        v. For members that are 18 years of age or older, treatment with pitolisant (Wakix) has been ineffective, contraindicated, or not tolerated; **OR**
    2. **Narcolepsy with excessive daytime sleepiness**; **AND**
        i. Member is seven years of age or older; **OR**
            a. If the request is for sodium oxybate ER (Lumryz), member is 18 years of age or older; **AND**
        ii. Confirmation of diagnosis with a sleep study (including polysomnography and multiple sleep latency test); **AND**
        iii. Symptoms have been present for at least three months; **AND**
        iv. Documented impairment/limitation of activities of daily living (e.g. missing school/work, household chores, driving); **AND**
        v. For members that are 18 years of age or older, treatment with ALL of the following has been ineffective, contraindicated, or not tolerated:
            a. Modafinil (Provigil) or armodafinil (Nuvigil); **AND**
            b. Solriamfetol (Sunosi); **AND**
            c. Pitolisant (Wakix); **OR**
    3. **Idiopathic hypersomnia**; **AND**
        i. Member is 18 years of age or older; **AND**
        ii. Provider attestation that hypersomnia is not better explained by medical or neurological disorder, mental disorder, medication use, or substance use disorder; **AND**
        iii. Provider attestation that diagnosis has been confirmed via the following:
            a. Polysomnography; **AND**
            b. Multiple sleep latency test; **AND**
        iv. Treatment with ALL of the following has been ineffective, contraindicated, or not tolerated:
            a. Modafinil (Provigil) or armodafinil (Nuvigil); **AND**
            b. Methylphenidate, amphetamine salts, or dextroamphetamine

II. Sodium oxybate (Xyrem, Lumryz) and calcium, magnesium, potassium, sodium oxybates (Xywav) are considered investigational when used for all other conditions, including but not limited to:
    A. Fibromyalgia
    B. Insomnia

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (e.g., reduction in cataplexy attacks, improvement in ability to complete activities of daily living, improvement in ability to stay awake); **AND**
IV. Medication will not be used in combination with sedative hypnotic agents (e.g., benzodiazepines, barbiturates, zolpidem tartrate)

Supporting Evidence

I. The American Academy of Sleep Medicine clinical practice guideline (2021) establishes clinical practice recommendations for treatment of central disorders of hypersomnolence. In adults with narcolepsy, there is a strong recommendation for modafinil, pitolisant, sodium oxybate, and solriamfetol for the treatment of narcolepsy in adults. There is a conditional recommendation for armodafinil, dextroamphetamine, and methylphenidate for the treatment of narcolepsy in adults. For pediatric patients with narcolepsy, the guidelines place a conditional recommendation for modafinil and sodium oxybate. Guidelines have not been updated to include calcium, magnesium, potassium, sodium oxybates (Xywav) or once nightly sodium oxybate ER (Lumryz) at this time.
II. The agents in this policy are a part of a REMS program which only allows certified prescribers and pharmacies to dispense sodium oxybate (Xyrem, Lumryz) and calcium, magnesium, potassium, sodium oxybates (Xywav). Prescribers must screen each patient for a history of alcohol or substance abuse, sleep-related breathing disorders, compromised respiratory function, depression or suicidality, and concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents.
III. Sodium oxybate (Xyrem, Lumryz) and calcium, magnesium, potassium, sodium oxybates (Xywav) are contraindicated in patients taking sedative hypnotic agents (e.g., benzodiazepines, barbiturates, zolpidem tartrate), and in patients with a succinic semialdehyde dehydrogenase deficiency. Sodium oxybate (Xyrem, Lumryz) and calcium, magnesium, potassium, sodium oxybates (Xywav) have serious side effects such as, central nervous system depression, abuse and misuse, respiratory depression and sleep-disordered breathing, depression and suicidality, parasomnias, other psychiatric reactions (e.g., anxiety, hallucinations, psychosis), and elevates salt content (use with caution in patients that have heart failure, hypertension, or renal impairment).
IV. Outside of salt content, there is no clinical difference between sodium oxybate (Xyrem) and calcium, magnesium, potassium, sodium oxybates (Xywav). Both agents are oral solutions taken twice nightly. Sodium oxybate (Lumryz) is an extended-release oral powder for suspension that is taken once nightly and contains the same active ingredient as sodium oxybate (Xyrem). Although falls while receiving oxybate treatment have been reported in clinical trials and post-marketing reports, no basis exists to attribute an increased risk of falls to a second nightly dose. Furthermore, each products drug information label discourages getting out of bed after any

oxybate dosing due to sedation. Pitolisant (Wakix) is FDA-approved for the treatment of cataplexy or excessive daytime sleepiness in adults with narcolepsy. Solriamfetol (Sunosi) is FDA-approved for the treatment of excessive daytime sleepiness associated with OSA and narcolepsy in adults.

V. There are no direct head-to-head studies comparing pitolisant (Wakix), solriamfetol (Sunosi), sodium oxybate (Xyrem, Lumryz), and calcium, magnesium, potassium, sodium oxybates (Xywav) to establish superior safety or efficacy of one product over the other. However, there are substantial cost differences between products despite not having any evidence of improved clinical efficacy or safety.

Narcolepsy with cataplexy/excessive daytime sleepiness:

I. Patients included in clinical trials had a history of narcolepsy for three months or greater and had chronic narcolepsy that was ongoing.

II. For the treatment of narcolepsy with cataplexy, sodium oxybate (Xyrem) was evaluated in two randomized, double-blind, placebo-controlled, multicenter, parallel-group trials with a total of 191 patients. Over 80% of patients in these trials were on stimulants as background therapy. The primary efficacy endpoint was the median change from baseline in cataplexy attacks. The baseline number of cataplexy attacks was 20 and 23 for the placebo group and Xyrem 9g group, respectively. Trial one had a reduction of 16 attacks per week in the 9g treatment group and 4 attacks per week in the placebo group ($p=0.0016$). Trial two was a randomized withdrawal trial, and the placebo group had 21 attacks within two weeks, while the sodium oxybate (Xyrem) group had zero attacks within two weeks ($p<0.001$).

III. For the treatment of narcolepsy with excessive daytime sleepiness, sodium oxybate (Xyrem) was evaluated in two randomized, double-blind, placebo-controlled trials with a total of 450 patients. The primary efficacy endpoint for trial three was the change from baseline in the Epworth Sleepiness Scale (EPSS). Sodium oxybate (Xyrem) had a -2 and -5 median change from baseline at week 8 for the 6g and 9g treatment groups, and both groups had statistically greater reductions than the placebo group ($p<0.001$). The primary efficacy endpoint for trial four was the change from baseline in the Maintenance of Wakefulness Test (MWT). Sodium oxybate (Xyrem) had a mean change from baseline of 0.6 compared to -2.7 for placebo at week 8 ($p<0.001$).

IV. For the treatment of narcolepsy with cataplexy and excessive daytime sleepiness in pediatrics, sodium oxybate (Xyrem) was evaluated in one double-blind, placebo-controlled, randomized-withdrawal trial with 106 pediatric patients. Patients included in this study were seven to 16 years of age. The primary efficacy endpoints were the change in the frequency of cataplexy attacks and EPSS. The median change from baseline in the number of cataplexy attacks per week was 0.3 for sodium oxybate (Xyrem) compared to 12.7 for placebo ($p<0.0001$). The median change in the EPSS was zero for sodium oxybate (Xyrem) and three for placebo ($p=0.0004$).

V. Sodium oxybate (Lumryz) is FDA-approved for treatment of narcolepsy with cataplexy and excessive daytime sleepiness in adults. Safety and efficacy was evaluated in the REST-ON trial, a double-blind, randomized, placebo-controlled trial that evaluated once nightly administration of sodium oxybate (Lumryz) in 212 patients with narcolepsy 16 years of age or older. Patients were randomized 1:1 to receive sodium oxybate (Lumryz) or placebo. The study was consisted of 13-weeks of treatment of escalating doses (g/night) of sodium oxybate (Lumryz) at 4.5 g week 1, 6 g weeks 2–3, 7.5 g weeks 4–8, and 9 g weeks 9–13. The three co-primary endpoints were the

maintenance of wakefulness test (MWT), clinical global Impression-improvement (CGI-I), and mean change in weekly cataplexy attacks. A statistically significant improvement was seen on the MWT, CGI-I, and mean weekly cataplexy attacks, for the 6 g (Week 3), 7.5 g (Week 8), and 9 g (Week 13) dose of sodium oxybate (Lumryz) compared to the placebo group ($p<0.001$).

VI. Solriamfetol (Sunosi) is FDA-approved for the treatment of excessive daytime sleepiness associated with OSA and narcolepsy in adults. The efficacy and safety of solriamfetol (Sunosi) was established in two Phase 3, multi-center, double-blind, placebo-controlled, randomized trials of fair quality that evaluated the use of solriamfetol (Sunosi) in patients with excessive daytime sleepiness associated with OSA (n=459) or either type I or type II narcolepsy (n=231). Solriamfetol (Sunosi) demonstrated a change in MWT of 7.7 minutes from baseline, and a change in EPSS of -3.8 from baseline, at week 12 ($p<0.0001$) for both endpoints against placebo.

VII. The efficacy and safety of calcium, magnesium, potassium, sodium oxybates (Xywav) was established in a Phase 3, multi-center, double-blind, placebo-controlled, randomized trial that evaluated the use of calcium, magnesium, potassium, sodium oxybates (Xywav) in patients with narcolepsy with cataplexy. Patients were all transitioned to the use of calcium, magnesium, potassium, sodium oxybates (Xywav) and optimized regardless of prior anti-cataplectic therapy or being naïve to treatment (n=201). Once optimized, efficacy was confirmed in the double blind, randomized withdrawal period (DB RWP) of this trial. During the DB RWP, outcomes showed a statistically significant worsening of cataplexy symptoms in patients on placebo when compared to those in the calcium, magnesium, potassium, sodium oxybates (Xywav) arm. The safety profile in pediatric patients with Xywav is expected to be similar to that of adult patients treated with Xywav and to that of pediatric patients treated with Xyrem.

VIII. Pitolisant (Wakix) is FDA-approved for the treatment of cataplexy or excessive daytime sleepiness in adults with narcolepsy. The efficacy of pitolisant (Wakix) was established in three randomized controlled trials (HARMONY I, I bis, and III), and one open-label, single-arm, long term safety & efficacy trial, in a total of 468 patients with excessive daytime sleepiness. The use of pitolisant (Wakix) in the treatment of narcolepsy with cataplexy was established in HARMONY CTP with supporting evidence in HARMONY I.

- In HARMONY I (n = 95): The primary efficacy outcome was the change in the Epworth Sleepiness Scale (ESS) score after eight weeks. Pitolisant (Wakix) 35.6 mg demonstrated a statistically greater reduction in the ESS score compared to placebo (change of -3.1 points [-5.73, -0.46]). When compared to modafinil, pitolisant (Wakix) failed to demonstrate non-inferiority for changes in ESS score.
- HARMONY I bis (n = 165): The primary efficacy outcome was the change in the ESS score and compared pitolisant (Wakix) 17.4 mg vs. placebo. Pitolisant (Wakix) demonstrated statistically significant reduction in the ESS score compared to placebo (change of -2.12 points [-4.10, -0.14]). When compared to modafinil, pitolisant (Wakix) failed to demonstrate non-inferiority for changes in ESS score.
- HARMONY III (n = 102): Efficacy was a secondary endpoint and was measured by the change in the ESS score from baseline to one year. The mean decrease in ESS scores was -4.6 ± 0.59 (-5.82, -3.44).
- HARMONY CTP (n = 106): The primary efficacy outcome was the change in the average number of cataplexy attacks per week as documented by patient diaries.

The cataplexy ratio rate was 0.51 (0.44-0.60, p<0.0001) for pitolisant (Wakix) compared to placebo.

Idiopathic Hypersomnia:

I. While sodium oxybate (Xyrem, Lumryz) does not carry an FDA approved indication for use in idiopathic hypersomnia (IH), the active moiety is the same as calcium, magnesium, potassium, sodium oxybates (Xywav). The chemical entity found in both of these products is expected to produce similar efficacy and safety for the treatment of IH.

II. The safety profile of calcium, magnesium, potassium, sodium oxybates (Xywav) and sodium oxybate (Xyrem, Lumryz) in pediatric patients for the treatment of IH has not been established.

III. Idiopathic hypersomnia (IH) is a sleep disorder that presents as chronic excessive daytime sleepiness (EDS) and difficulty waking up from nighttime sleep or daytime naps. Symptomatic patients are unable to maintain wakefulness and alertness during major waking episodes of the day, with sleep occurring unintentionally. Diagnosis of IH is made by objective sleep tests as well as ruling out other sleep disorders, medical or psychiatric disorders, or use of drugs that may be causing EDS. Hypersomnia associated with psychiatric disorders (i.e., atypical depression, bipolar depression, dysthymia, etc.) is a differential diagnosis and commonly overlaps with complaints of excessive daytime sleepiness and may be mistaken for idiopathic hypersomnia if not ruled out. In patients where hypersomnia may be better explained by other sleep disorders, psychiatric disorders, or use of certain medications, use of sodium oxybate (Xyrem) and calcium, magnesium, potassium, sodium (Xywav) is not considered medically necessary, as treatment of hypersomnia in this setting is guided by correcting the underlying cause.

IV. IH is diagnosed through combined evaluation of nocturnal polysomnography and a multiple sleep latency test (MSLT). Polysomnography can exclude causes of excessive daytime sleepiness (i.e., subtle forms of obstructive sleep apnea) while shortened mean sleep latency and the number of sleep-onset rapid eye movement sleep periods (SOREMPs) can distinguish between narcolepsy and IH.

V. Stimulants and alerting agents (i.e., modafinil, armodafinil, methylphenidate, amphetamine salts) for IH are recommended based on experience with these medications in the setting of excessive daytime sleepiness (EDS) associated with narcolepsy. FDA approval of stimulants and alerting agents in related sleep conditions such as narcolepsy, American Academy of Sleep Medicine clinical guideline recommendations, large body of safety data, and proven effects on EDS support the use of stimulants and alerting agents in IH. Additionally, the majority of clinical trial population for calcium, magnesium, potassium, sodium oxybates (Xywav) were on a stimulant/alerting agent at baseline. Given the known safety profile, extensive clinical use, and cost-effectiveness of these therapies, a trial of stimulants and alerting agents is required.

VI. The efficacy and safety of calcium, magnesium, potassium, sodium oxybates (Xywav) was established in a Phase 3, interventional, double-blind, placebo-controlled, randomized withdrawal trial that evaluated the use of calcium, magnesium, potassium, sodium oxybates (Xywav) in adult patients with IH. Participants were a median age of 39 years, 71% female, 81% white and non-Hispanic or Latino. At baseline 2% of patients were taking Xyrem only, 4% were taking Xyrem in addition to another stimulant/alerting agent, 54% were taking a stimulant/alerting agent, and 41% were naïve to therapy. CNS stimulants were allowed to continue throughout the SDP and DB RWP – this occurred in 57% of patients. Baseline Epworth Sleepiness Scale ESS scores were 16 in calcium, magnesium, potassium, sodium oxybates

(Xywav) and 17 in the placebo groups. Efficacy was confirmed in the double blind, randomized, 2-week withdrawal period (DB RWP). Primary outcome showed a statistically significant worsening of median ESS in patients on placebo (Δ 5 to 14 points) when compared to those in the calcium, magnesium, potassium, sodium oxybates (Xywav) arm (Δ 6.5 to 7 points) ($p<0.0001$).

VII. No new safety signals were seen in calcium, magnesium, potassium, sodium oxybates (Xywav) for its evaluation for use in IH. The most commonly reported adverse events were nausea (21%), headache (16%), anxiety (12%), dizziness (12%), insomnia (9%), hyperhidrosis (8%), decreased appetite (8%), vomiting (7%), and dry mouth (6%). Across all study periods (excluding placebo-controlled patients during DB RWP) 17 (11%) reported adverse effects that led to withdrawal from the study (e.g., anxiety, nausea, insomnia, fatigue, feeling abnormal, fall, decreased appetite, dizziness, parathesis, tremor, parasomnia, confused state, hallucination (visual), and irritability). TEAEs leading to discontinuation that were reported by >1 participant included anxiety (n=4), insomnia (n=3), nausea (n=3), and confusion (n=2).

VIII. The calcium, magnesium, potassium, sodium oxybates (Xywav) study population included patients previously treated with stimulant/alerting therapy and allowed patients to continue these agents throughout the study. There is evidence to support concominant use of stimulants and alerting agents (i.e., methylphenidate, solriamfetol, modafinil, etc.) with calcium, magnesium, potassium, sodium oxybates (Xywav) or sodium oxybate (Xyrem, Lumryz).

Investigational or Not Medically Necessary Uses

I. Sodium oxybate (Xyrem, Lumryz) and calcium, magnesium, potassium, sodium oxybates (Xywav) have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Fibromyalgia
   B. Insomnia

Appendix

I. Treatment Table

	Narcolepsy with cataplexy (type I)	Narcolepsy without cataplexy (type 2)	EDS w/ narcolepsy	EDS w/ OSA	IH
Generic sodium oxybate	X		X*		X†
Xyrem IR oral soln	X		X*		X†
Lumryz ER oral susp	X		X		X†
Xywav	X*		X*		X
Wakix	X	X	X		
Sunosi		X	X	X	
*Adult + Pediatric indication (patients >7yo) † used off label per policy					

II. Dose conversion for patients switching from twice nightly oxybate to once nightly sodium oxybate (Lumryz)
   a. Switching from immediate-release sodium oxybate solution, patients may be switched to sodium oxybate extended-release at the nearest equivalent dosage in grams per night (e.g., 7.5 g sodium oxybate divided in 2 doses to 7.5 g sodium oxybate extended-release once per night)

III. Sodium content

a. Xyrem Sodium content: 820 mg of sodium per 4.5-g dose of sodium oxybate immediate-release oral solution
b. Lumryz Sodium content: 820 mg of sodium per 4.5-g dose of sodium oxybate extended-release oral suspension
c. Xywav Sodium content: 131 mg of sodium per 9-g dose of calcium, magnesium, potassium, sodium oxybates (Xywav)

References

1. Xyrem [Prescribing Information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. April 2023.
2. SUNOSI [Prescribing Information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. June 2023.
3. Scammell TE. Treatment of narcolepsy in adults. UpToDate Inc. https://www.uptodate.com. (Accessed on April 27, 2020.)
4. Scammell TE. Clinical features and diagnosis of narcolepsy in adults. UpToDate Inc. https://www.uptodate.com. Accessed on April 27, 2020.
5. Morgenthaler TI, Kapur VK, Brown T, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. Sleep. 2007;30(12):1705-11.
6. XyremREMS. Xyrem REMS Program. https://www.xyremrems.com/. Accessed April 27, 2020.
7. Chervin RD. Idiopathic hypersomnia. UpToDate Inc. https://www.uptodate.com. Accessed on September 24, 2021.
8. Freedman N. Quantifying sleepiness. UpToDate Inc. https://www.uptodate.com. Accessed on September 24, 2021.
9. Xywav [Prescribing Information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. April 2023.
10. Maski K, Trotti LM, Kotagal S, et al. Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2021;17(9):1881–1893.
11. LUMRYZ [Prescribing Information]. Chesterfield, MO: Avadel CNS Pharmaceutical, LLC. May 2023.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
solriamfetol (Sunosi); pitolisant (Wakix) Policy	Narcolepsy with or without cataplexy
	Excessive daytime sleepiness associated with narcolepsy
	Excessive sleepiness associated with OSA

Policy Implementation/Update

Action and Summary of Changes	Date
Added sodium oxybate (Lumryz) into policy. Aligned Xywav with sodium oxybate, Xyrem, Lumryz. Removed criteria requiring trial of Xyrem and FDA labeled contraindication to Xyrem or sensitive to sodium intake if request is for Xywav. Added trial of Wakix for adults with narcolepsy indications. Added trial of generic sodium oxybate prior to Xyrem. Updated supporting evidence and references. Added appendix table, related policies.	08/2023
Addition of authorized generic sodium oxybate into policy.	02/2023
Added criteria for new indication for idiopathic hypersomnia (IH). Removal of idiopathic hypersomnia from Investigational or Not Medically Necessary Uses section. Added IH criteria to both Xyrem and Xywav sections for policy. Updates to supporting evidence.	12/2021
Updated route of approval of Xywav to require trial of Wakix; updated language around trial of Xyrem prior to Xywav to require member has a FDA labeled contraindication or intolerance to Xyrem OR member is sensitive to sodium intake and provider attests dietary salt intake cannot be reduced further. Updates to supporting evidence.	04/2021

Removed need to trial and fail stimulates prior to use with Xyrem for Narcolepsy with excessive daytime sleepiness	01/2021
Update to add new to market Xywav with requirement to trial and fail or demonstrate contraindication or intolerance to Xyrem. Updated clinical trial background on Xywav.	10/2020
Transitioned from criteria to policy. Included information on: • Requirement to be prescribed by or in consultation with a sleep specialist, psychiatrist, or neurologist • Confirmation of diagnosis for narcolepsy • Requirement for chronic narcolepsy defined as three-month history • Requirement that member has functional impairment for activities of daily living • Updated requirements for trial and failure to one stimulant, and modafinil or armodafinil, and Sunosi	05/2020
Policy created	02/2012

Policy Type: PA/SP Pharmacy Coverage Policy: UMP060

Description
Solriamfetol (Sunosi) is a dopamine and norepinephrine reuptake inhibitor (DNRI).
Pitolisant (Wakix) is a histamine-3 receptor antagonist/reverse agonist.

Length of Authorization
- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
solriamfetol (Sunosi)	75 mg tablets	Excessive sleepiness associated with either OSA or narcolepsy	60 tablets/30 days
	150 mg tablets		30 tablets/30 days
pitolisant (Wakix)	4.45 mg tablets	Excessive daytime sleepiness associated with narcolepsy or narcolepsy with cataplexy	14 tablets/7 days
	17.8 mg tablets		60 tablets/30 days

Initial Evaluation

I. Solriamfetol (Sunosi) and pitolisant (Wakix) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a sleep specialist, psychiatrist, or neurologist; **AND**
   C. A diagnosis of one of the following:
      1. **Excessive daytime sleepiness; AND**
         i. **Narcolepsy <u>without cataplexy</u>; AND**
            a. Treatment with the following has been ineffective, contraindicated, or not tolerated:
               i. Stimulant (e.g., methylphenidate, amphetamine, etc.); **AND**
               ii. Modafinil or armodafinil; **AND**
               iii. If the request is for pitolisant (Wakix): Treatment with solriamfetol (Sunosi) has been ineffective, contraindicated, or not tolerated; **OR**
         ii. **Obstructive sleep apnea (OSA)**; **AND**
            a. The request is for solriamfetol (Sunosi); **AND**

b. The member has current or prior use of a primary OSA therapy (e.g., CPAP, mandibular advancement device or surgical intervention); **AND**
c. Treatment with modafinil or armodafinil has been ineffective, contraindicated, or not tolerated

2. **Narcolepsy <u>with cataplexy</u>; AND**
   i. The request is for pitolisant (Wakix); **AND**
   ii. Confirmation of cataplexy defined as episodes of sudden loss of muscle tone; **AND**
   iii. Documented impairment/limitation of activities of daily living (e.g. missing school/work, household chores, driving).

II. Solriamfetol (Sunosi) and pitolisant (Wakix) are considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   1. Excessive sleepiness associated with Parkinson's Disease or glioblastoma
   2. Shift work sleep disorder (SWSD)
   3. Attention-deficit/hyperactivity disorder (ADHD)
   4. Fatigue not related to narcolepsy or OSA

   A. Solriamfetol (Sunosi)
      1. Major depressive disorder
      2. Steinert myotonic dystrophy syndrome

   B. Pitolisant (Wakix)
      1. Excessive daytime sleepiness associated with obstructive sleep apnea

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms [e.g., reduction in cataplexy attacks, improvement in ability to complete activities of daily living, improvement in ability to stay awake)

Supporting Evidence

I. Solriamfetol (Sunosi) is FDA-approved for the treatment of excessive daytime sleepiness associated with OSA and narcolepsy in adults.
II. The efficacy and safety of solriamfetol (Sunosi) was established in two Phase 3, multi-center, double-blind, placebo-controlled, randomized trials of fair quality that evaluated the use of solriamfetol (Sunosi) in patients with excessive daytime sleepiness associated with OSA (n=459) or either type I or type II narcolepsy (n=231).

III. In clinical trials, patients with OSA were required to be stable for greater than one month on primary OSA therapy (e.g. CPAP, mandibular advancement device, or surgical intervention) prior to use of solriamfetol (Sunosi).
IV. Stimulants such as amphetamine have not been studied in OSA.
V. Current guidelines for patients with excessive sleepiness associated with narcolepsy recommend modafinil or armodafinil as first-line treatment options. Stimulants are recommended as second line therapy.
VI. The current FDA maximum dose for solriamfetol (Sunosi) is 150 mg per day. Although doses of 300 mg were studied, the 300 mg dose was not approved due to tolerability concerns.
VII. Pitolisant (Wakix) is FDA-approved for the treatment of excessive daytime sleepiness in adults with narcolepsy. Pitolisant (Wakix) is the only agent for the treatment of narcolepsy that is not scheduled at this time. Pitolisant (Wakix) was studied in three randomized controlled trials, and one open-label, single-arm, long term safety & efficacy trial, in a total of 468 patients with EDS. HARMONY I and I bis included modafinil as an active comparator to pitolisant (Wakix).
VIII. HARMONY I (n = 95): The primary efficacy outcome was the change in the Epworth Sleepiness Scale (ESS) score after eight weeks. Pitolisant (Wakix) 35.6 mg demonstrated a statistically greater reduction in the ESS score compared to placebo (change of -3.1 points [-5.73, -0.46]). When compared to modafinil, pitolisant (Wakix) failed to demonstrate non-inferiority for changes in ESS score. The ESS score has been commonly used in standard practice and was originally validated through a study in 1991.
IX. HARMONY I bis (n = 165): The primary efficacy outcome was the change in the ESS score and compared pitolisant (Wakix) 17.4 mg vs. placebo. Pitolisant (Wakix) demonstrated statistically significant reduction in the ESS score compared to placebo (change of -2.12 points [-4.10, -0.14]). When compared to modafinil, pitolisant (Wakix) failed to demonstrate non-inferiority for changes in ESS score.
X. HARMONY CTP (n = 106): The primary efficacy outcome was the change in the average number of cataplexy attacks per week as documented by patient diaries. The cataplexy ratio rate was 0.51 (0.44-0.60, p<0.0001) for pitolisant (Wakix) compared to placebo.
XI. HARMONY III (n = 102): Efficacy was a secondary endpoint and was measured by the change in the ESS score from baseline to one year. The mean decrease in ESS scores was -4.6 ± 0.59 (-5.82, -3.44).
XII. Pitolisant (Wakix) has a noted contraindication for patients with severe hepatic impairment, as well as a warnings and precaution for QTc prolongation. Common side effects were headache, insomnia, irritability, anxiety, and nausea. Less common side effects of musculoskeletal pain, upper respiratory tract infection, heart rate increase, hallucinations, abdominal pain, sleep disturbance, and decreased appetite were also noted.
XIII. There are no direct head-to-head studies comparing pitolisant (Wakix) and solriamfetol (Sunosi) to establish superior safety or efficacy of one product over the other; however, pitolisant (Wakix) is significantly more costly than solriamfetol (Sunosi) despite not having any evidence of improved clinical efficacy or safety.
XIV. The use of pitolisant (Wakix) in the treatment of narcolepsy with cataplexy was established in HARMONY CTP with supporting evidence in HARMONY I. Primary outcomes of HARMONY CTP evaluated weekly rate of cataplexy (WRC) while HARMONY I, Daily Rate of Cataplexy (DRC) was

evaluated as a secondary endpoint to support the use in cataplexy. Secondary outcomes of DRC in HARMONY I showed a significant improvement DRC.

Investigational or Not Medically Necessary Uses

I. Solriamfetol (Sunosi) and pitolisant (Wakix) currently have no evidence supporting efficacy or safety in the following conditions:
   A. Shift work sleep disorder (SWSD)
   B. Attention-deficit/hyperactivity disorder (ADHD)
   C. Fatigue not related to narcolepsy or OSA
   D. Excessive sleepiness associated with Parkinson's Disease

II. Solriamfetol (Sunosi) has not been studied in the following indications:
   A. Major depressive disorder
   B. Steinert myotonic dystrophy syndrome

III. Pitolisant (Wakix) is currently being studied for use in excessive daytime sleepiness in patients with obstructive sleep apnea, however, there is currently a lack of sufficient safety and efficacy information to support use in this condition.

References

1. SUNOSI (solriamfetol) tablets, for oral use. Prescribing Information. Palo Alto, CA. Jazz
2. Thorpy M, Shapiro C, Mayer G, et al. A Randomized Study of Solriamfetol for Excessive Sleepiness in Narcolepsy. Annals of Neurology. 2019; 85:359-370.
3. Schweitzer PK, Rosenberg R, Zammit GK, Gotfried M, Chen D, Carter LP et al. Solriamfetol for Excessive Sleepiness in Obstructive Sleep Apnea (TONES 3): A Randomized Controlled Trial. Am J Respir Crit Care Med. 2018 Dec 6. doi: 10.1164/rccm.201806-1100OC.
4. Wakix (pitolisant) [Prescribing Information]. Harmony Biosciences, LLC: Plymouth Meeting, PA. August 2019.
5. Wakix (pitolisant) [Formulary Dossier]. Harmony Biosciences, LLC: Plymouth Meeting, PA. September 2019.
6. Dauvilliers Y, Bassetti C, Lammers GJ, et al. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomized trial. Lancet Neurol. 2013; 12: 1068–75.
7. Dauvilliers Y, Arnulf I, Szakacs Z, et al. Long-term use of pitolisant to treat patients with narcolepsy: Harmony III Study. Sleep. 2019.
8. Szakacs Z, Dauvilliers Y, Mikhaylov V, et al. Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomized, double-blind, placebo-controlled trial. Lancet Neurol. 2017; 16: 200–07.
9. Dauvilliers Y, Bassetti C, Lammers GJ, et al. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. Lancet Neurol. 2013;12(11):1068-1075.
1. Zoltan Szakacs, Yves Dauvilliers, et. al. Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial (HARMONY CTP). Lancet Neurol 2017; 16: 200–07

Policy Implementation/Update:

Action and Summary of Changes	Date
Removed criteria "Use will not be in combination with sodium oxybate (Xyrem) or calcium, magnesium, potassium, sodium oxybates (Xywav)" After going into the different mechanisms of these drugs, clinical trials, and consulting the team, it was decided that these drugs can be used in combination with each other	12/2021
Updated policy to include new indication for Wakix use in patients with narcolepsy with cataplexy.	12/2020

Updated policy to require trial and failure of solriamfetol (Sunosi) prior to approval of pitolisant (Wakix) for narcolepsy.	06/2020
Addition of pitolisant (Wakix) information for coverage including: experimental/investigational, coverage for narcolepsy, quantity limits, and evidence base.	09/2019
New policy for solriamfetol (Sunosi).	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP153

Split Fill Management*

Description

Sonidegib (Odomzo) is an orally administered Hedgehog pathway inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
sonidegib (Odomzo)	200 mg capsule	Basal cell carcinoma of the skin, locally advanced	30 capsules/30 days

Initial Evaluation

I. Sonidegib (Odomzo) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist or dermatologist; **AND**
   C. Sonidegib (Odomzo) will not be used in combination with any other oncologic medication; **AND**
   D. A diagnosis of **locally advanced basal cell carcinoma (BCC)** when the following are met:
      1. Basal cell carcinoma has recurred or progressed after radiation or surgery, unless both are contraindicated; **AND**
      2. The member has not progressed on any other oncologic medication (e.g., has not progressed on vismodegib [Erivedge]); **AND**
      3. Provider attestation that the member, either male or female, has been counseled on the teratogenicity and embryo-fetal toxicity risks with sonidegib (Odomzo).

II. Sonidegib (Odomzo) is considered investigational when used for all other conditions, including but not limited to:
   A. Metastatic basal cell carcinoma
   B. Acute leukemia
   C. Breast cancer
   D. Medulloblastoma
   E. Multiple myeloma
   F. Myelofibrosis

G. Prostate cancer
H. Breast cancer
I. Ovarian cancer
J. Graft versus host disease
K. Pancreatic cancer
L. Lung cancer
M. Hepatocellular carcinoma

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Sonidegib (Odomzo) is prescribed by, or in consultation with, an oncologist or dermatologist; **AND**
IV. A diagnosis of **locally advanced basal cell carcinoma**; **AND**
    A. Clinical response to therapy, such as improvement or stabilization of disease, or decrease or stabilization of tumor size or spread; **AND**
    B. Provider attestation that the member, either male or female, has been counseled on the teratogenicity and embryo-fetal toxicity risks with sonidegib (Odomzo).

Supporting Evidence

I. The safety and efficacy of sonidegib (Odomzo) was evaluated in a single, double-blind, single-drug trial. Those included had a diagnosis of locally advanced basal cell carcinoma (laBCC), and 144 adult subjects were randomized (2:1) to receive sonidegib (Odomzo) 800 mg or 200 mg daily. To be included in the trial, subjects were required to have lesions for which radiotherapy was contraindicated or inappropriate (e.g., limitations due to tumor location), that had recurred after radiotherapy, had unresectable disease in which surgical resection would result in substantial deformity, or that had recurred after prior surgical resection. The primary outcome was objective response rate (ORR) which was determined by a blinded central review committee according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST). A secondary measure was duration of response (DoR). The ORR was 56% (CI 43-68), and consisted of three (5%) complete responders, and 34 (52%) partial responders. The median duration of response was 26.1%; however, due to the single-drug nature of the trial, these results should be interpreted with caution.
II. There were 128 subjects randomized to sonidegib (Odomzo) 800 mg daily. There was a lack of further benefit over the 200 mg dose relative to the safety profile.
III. Sonidegib (Odomzo) carries a black box warning for embryo-fetal death or severe birth defects when administered to a pregnant woman. It is noted in the medication label that pregnancy be ruled out prior to initiating therapy. Those of reproductive potential should use contraception during treatment and for at least 20 months following the last dose. Males carry of risk of

exposure through semen; thus, the package label recommends use of condoms with female partners during medication exposure and for at least eight months after the last dose.

IV. Vismodegib (Erivedge) is FDA-approved for adults with metastatic and locally advanced basal cell carcinoma. Erivedge has an overlapping indication with sonidegib (Odomzo), and if disease progression has occurred on or after one of these therapies, there is currently insufficient evidence regarding safety and/or efficacy of the other. One published piece of literature evaluated sonidegib (Odomzo) in those that were resistant to vismodegib (Erivedge); however, this trial included only nine subjects all of which showed no response to sonidegib (Odomzo) or were not evaluable for safety and/or efficacy. Available evidence disfavors use of sequential Hedgehog pathway inhibitors.

Investigational or Not Medically Necessary Uses

I. There is currently insufficient evidence to support safety and/or efficacy of sonidegib (Odomzo) in the following settings:
   A. Metastatic basal cell carcinoma
   B. Acute leukemia
   C. Breast cancer
   D. Medulloblastoma
   E. Multiple myeloma
   F. Myelofibrosis
   G. Prostate cancer
   H. Breast cancer
   I. Ovarian cancer
   J. Graft versus host disease
   K. Pancreatic cancer
   L. Lung cancer
   M. Hepatocellular carcinoma

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Odomzo [Package Insert]. Cranbury, NJ. Sun Pharmaceutical Industries, Inc. 2017.
2. Burness CB, Scott LJ. Sonidegib: A Review in Locally Advanced Basal Cell Carcinoma. Target Oncol. 2016;11(2):239-46.
3. Danial C., Sarin K. Oro A., et al. An investigator-initiated open-label trial of sonidegib in advanced basal cell carcinoma patients resistant to vismodegib. Clin Cancer Res. 2016;22: 1325-1329.

Policy Implementation/Update:

Date Created	October 2015
Date Effective	November 2015
Last Updated	November 2019
Last Reviewed	November 2019

Action and Summary of Changes	Date
Prior authorization transitioned to policy. Addition of age edit, clarification and addition of requirements regarding previous therapies and use of sonidegib (Odomzo) monotherapy. Renewal duration increased for six to 12 months.	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP244

Split Fill Management*

Description

Sotorasib (Lumakras) is an orally administered selective inhibitor of Kirsten Rat Sarcoma viral oncogene homologue (KRAS) and targets tumors harboring KRAS G12C mutation.

Length of Authorization

- N/A

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
sotorasib (Lumakras)	120 mg tablets	Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with a KRAS G12C mutation	240 tablets/30 days

Initial Evaluation

I. Sotorasib (Lumakras) is considered investigational when used for all conditions, including but not limited to Non-Small Cell Lung cancer (NSCLC).

Renewal Evaluation

I. N/A

Supporting Evidence

I. Sotorasib (Lumakras) is the first therapy FDA-approved for advanced or metastatic NSCLC that harbors a KRAS G12C mutation. It is also the first orally administered drug in this setting.

II. KRAS mutations account for up to 25% of mutations in NSCLC and are often associated with resistance to targeted therapies and generally poor patient outcomes in patients with cancer. KRAS G12C, a subset of KRAS mutations, accounts for about 13% of mutations in NSCLC.

III. Most patients with NSCLC including *KRAS*-mutated tumors are treated with systemic chemotherapy, which includes carboplatin, pemetrexed, cisplatin, paclitaxel. Additionally, targeted immunotherapy such as inhibitors of programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1) (e.g., pembrolizumab (Keytruda), atezolizumab (Tecentriq), nivolumab (Opdivo)) are also recommended. Vascular Endothelial Growth Factor (VEGF) inhibitor ramucirumab (Cyramza) in combination with docetaxel (Taxotere) has shown success as a subsequent-line therapy in refractory disease.

IV. Sotorasib (Lumakras) received FDA-approval as a subsequent-line therapy in the advanced or metastatic NSCLC, after progression on or after at least one prior systemic chemotherapy. The National Comprehensive Cancer Network (NCCN) treatment guideline for NSCLC has given sotorasib (Lumakras) a Category 2A recommendation as a subsequent-line treatment for NSCLC harboring KRAS G12C mutation, after progression on or after conventional chemotherapy and / or immunotherapy.

V. Sotorasib (Lumakras) was evaluated in CodeBreak100, an ongoing Phase 1 / 2, open-label, single-arm trial. Patients (N=126) with KRAS G12C mutated NSCLC, who had disease progression after chemotherapy and/ or immunotherapy were included. All patients received sotorasib (Lumakras) 960 mg orally once a day for a median 15.3 months. Although this is an ongoing clinical trial with the goal to assess efficacy of sotorasib (Lumakras) for multiple oncological settings (NSCLC as well as other solid tumors harboring KRAS mutations), the FDA-approval for sotorasib (Lumakras) was based on outcomes from NSCLC cohort.

VI. The primary efficacy outcome for CodeBreak100 trial was Overall Response Rate (ORR). Key secondary outcomes were Progression-free Survival (PFS), duration of response (DoR), and Overall Survival (OS). Sotorasib (Lumakras) showed an ORR of 37.1% (95% CI; 28.6, 46.2), which included 3.2% complete responses (CR) and 33.9% partial responses (PR). Additionally, participants in this cohort showed DoR of 11.1 months (95% CI; 6.9, NE), PFS 6.8 months (95% CI; 5.1, 8.2), and OS 12.5 months (95% CI; 10.0, NE).

VII. Based on the data from CodeBreak100 trial, the quality of the evidence to support efficacy of sotorasib (Lumakras) is considered low at this time. Given the lack of comparator and single-arm open-label trial design, as well as lack of clinically meaningful outcomes in morbidity, mortality, and quality of life – medication efficacy remains uncertain.

VIII. The safety of sotorasib (Lumakras) was based on trial participants (n=126) exposed to therapy. The most common adverse events include diarrhea, nausea, fatigue, and aspartate aminotransferase increase. Serious adverse events (grade 3 or higher) occurred in 42.1% patients and included dyspnea, pneumonitis, and elevation of liver enzymes. At this time, patient population and duration of exposure to sotorasib (Lumakras) are limited to clinical trial participants. Thus, real-world safety profile and patient experience with this drug remain undefined. Based on single-arm, open-label clinical trial in small sample population, the overall safety profile of sotorasib (Lumakras) is largely unknown; thus, it is unknown at this time if benefits of this medication outweigh the risks.

IX. Currently, there are multiple clinical trials (Phase 1b / 2) ongoing for sotorasib (Lumakras) in the settings of NSCLC, colorectal cancer, and other solid tumors harboring KRAS G12C mutation. Additionally, sotorasib (Lumakras) is being studied as a combination regimen with other targeted therapies (e.g., MEK inhibitor, EGFR inhibitor, SHP2 inhibitor) for the treatment of NSCLC. These clinical trials are in early phases and data are not available for review.

X. Single-arm, open-label clinical trials may provide indicators of primary efficacy. However, data from these trials are insufficient to determine causal relationship between the drug use with patient outcomes and may not be clinically meaningful to make healthcare decisions. Additionally, the primary endpoint, ORR, despite being considered an optimal marker for a single-arm study design, is not a strong surrogate marker. Overall Response Rate (ORR) is not a direct measure of benefit and cannot be used as a comprehensive measure of drug activity.

XI. Targeted therapies for treatment of NSCLC have garnered interest in recent years and may be considered part of a paradigm shift in the management of NSCLC based on histology and actionable driver mutations. However, while initially effective, many targeted therapies have been associated with increased drug resistance after their initial use. Acquired resistance to

current molecularly targeted therapies in lung cancer presents a major clinical challenge. Additionally, targeted therapy approach is also susceptible to failure due to escape mutations.

XII. Ongoing research focuses on identifying potential novel biomarkers and mechanisms involved in resistance to these therapies. In this regard, conventional chemotherapy agents (e.g., docetaxel, pemetrexed) and immune checkpoint inhibitors (e.g., nivolumab, pembrolizumab) remain practical and established therapeutic options for members, after progression on or after first-line therapies (e.g., platinum-based chemotherapy). Additionally, combination regimens containing angiogenesis inhibitors with conventional chemotherapy agents (e.g., ramucirumab and docetaxel) has been successful treatment options based on a Phase 3 clinical trial reporting OS of 10.5 months versus docetaxel monotherapy 9.1 months (HR 0.86; 95% CI 0.75, 0.98; p 0.023). Efficacy and safety of sotorasib (Lumakras) in comparison with, or in combination with, currently established regimens, has not been studied and remains unknown.

XIII. Due to lack of conclusive clinical data to direct a path to curative therapies, NCCN guidelines for NSCLC notes that the best management for any patient with cancer is in a clinical trial setting, and participation in trial is especially encouraged. Patients participating in clinical trials receive regular care, often at leading health care facilities with experts in the field while participating in important medical research and further advancements in treatment, with close safety monitoring and follow-up. Participation in a clinical trial remains the most favorable treatment option for patients with advanced NSCLC. Despite the accelerated FDA-approval, and category 2A recommendation from NCCN, continued approval of sotorasib (Lumakras) as a second-line treatment of NSCLC, remains contingent upon verification of clinical benefit in confirmatory trials. As of August 2021, a Phase 3 randomized clinical trial (CodeBreak200) to assess efficacy and safety of sotorasib (Lumakras) in comparison with docetaxel, as a subsequent-line treatment for NSCLC, is underway. Additionally, expanded access program via manufacturer, as part of the ongoing clinical studies of sotorasib (Lumakras), remains a practical option and an alternative path to treatment for qualifying patients.

Investigational or Not Medically Necessary Uses

I. Sotorasib (Lumakras) has not been sufficiently studied for safety and efficacy for any condition to date.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Lumakras [Prescribing Information]. Amgen Pharmaceuticals Inc., Thousand Oaks, CA. June 2021.
2. Skoulidis F, Li BT, Dy GK et al. Sotorasib for Lung Cancers with *KRAS* p.G12C Mutation. N Engl J Med. 2021;384(25):2371-2381.
3. Black RC, Khurshid H. NSCLC: an update of driver mutations, their role in pathogenesis and clinical significance. R I Med J. (2013). 2015; 98: 25-8.
4. Aggarwal S, Whipple S, Hsu H, et al. 1339P: Clinicopathological characteristics and treatment patterns observed in real-world care in patients with advanced non-small cell lung cancer (NSCLC) and KRAS G12C mutations in the Flatiron Health (FH)-Foundation Medicine (FMI) Clinico-Genomic Database (CGDB). *Ann Oncol*. 2020;31: S860.

5. Hayashi H, Okamoto I, Taguri M, Morita S, & Nakagawa K. Post-progression survival in patients with advanced non-small-cell lung cancer who receive second-line or third-line chemotherapy. *Clin Lung Cancer*. 2013; 14:261-266.
6. National comprehensive Cancer Network. NCCN Guidelines: Non-small Cell Lung Cancer V5.2021. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated June 15, 2021.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP278

Description

Sparsentan (Filspari) is an orally administered dual endothelin (ET_AR) and angiotensin II (AT_1R) receptor antagonist (DEARA) and inhibits endothelin-1 and angiotensin II, which may contribute to pathogenesis of immunoglobulin A nephropathy (IgAN).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit*
sparsentan (Filspari)	Primary IgA nephropathy; at high risk of progression	200 mg tablet	30 tablets/30 days
		400 mg tablet	30 tablets/30 days

**Quantity limit exceptions are not allowed.*

Initial Evaluation

I. **Sparsentan (Filspari)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a nephrologist or immunologist; **AND**
   C. Medication will not be used in combination with an angiotensin converting enzyme (ACE) inhibitor (e.g., enalapril, lisinopril); angiotensin receptor blocker (ARB) (e.g., valsartan, irbesartan), or a corticosteroid (e.g., prednisone, methylprednisolone, budesonide (Tarpeyo)); **AND**
   D. A diagnosis of **Primary immunoglobulin A nephropathy (IgAN)** when the following are met:
      1. Diagnosis of Primary immunoglobulin A nephropathy (IgAN) has been confirmed by a kidney biopsy; **AND**
      2. Documentation of elevated protein levels in urine as indicated by proteinuria ≥ 1 g/day or urine protein to creatinine ratio (UPCR) ≥ 1.5 g/g; **AND**
      3. Treatment with one of the following therapies has been ineffective, not tolerated, or all are contraindicated:
         i. A renin-angiotensin system (RAS) inhibitor for ≥ 3 months [e.g., angiotensin converting enzyme (ACE) inhibitor (e.g., enalapril, lisinopril); angiotensin receptor blocker (ARB) (e.g., valsartan, irbesartan)]; **OR**
         ii. A systemic corticosteroid for ≥ 9 months (e.g., prednisone, methylprednisolone, budesonide)

II. Sparsentan (Filspari) is considered investigational when used for all other conditions, including but not limited to:
   A. Secondary IgA nephropathy
   B. Newly diagnosed IgAN without high risk of disease progression
   C. Sparsentan (Filspari) used in combination with IgAN-indicated budesonide (Tarpeyo)
   D. Focal segmental glomerulosclerosis (FSGS)
   E. Chronic kidney disease (CKD) other than primary IgAN

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication will be used as a monotherapy (i.e., not in combination with angiotensin converting enzyme (ACE) inhibitor (e.g., enalapril, lisinopril); angiotensin receptor blocker (ARB) (e.g., valsartan, irbesartan), or corticosteroid (e.g., prednisone, methylprednisolone, budesonide (Tarpeyo)); **AND**
IV. Documentation of renal labs including proteinuria or urine protein to creatinine ratio (UPCR) are obtained within 30 days of the date of renewal; **AND**
V. Member has exhibited improvement or stability of disease symptoms [e.g., reduction in proteinuria <1 g/day or urine protein to creatinine ratio (UPCR) < 1.5 g/g]

Supporting Evidence

I. Sparsentan (Filspari) is a novel Dual Endothelin Angiotensin Receptor Antagonist (DEARA) FDA-approved for the reduction of proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression. Sparsentan (Filspari) is an orally administered tablet given once daily. Sparsentan (Filspari) has not been studied in pediatric population.
II. Due to the complexities related to diagnosis monitoring and management of IgAN patients, therapy for this disease space should be initiated by or in consultation with a specialist such as nephrologist or immunologist.
III. IgAN, also called Berger's disease, is a rare kidney disorder characterized by deposits of immune complexes containing galactose-deficient IgA in the glomerular mesangium leading to glomerulosclerosis, and renal failure. Although previously considered a benign condition, IgAN is now recognized to cause end-stage renal disease (ESRD) in 30% of affected individuals.
IV. The Kidney Disease Improving Global Outcomes (KDIGO) guideline indicates IgAN can only be diagnosed with a kidney biopsy. While there are several prognostic scoring tools that have been developed to assist in predicting kidney outcomes of IgAN patients (i.e., MEST-C, International IgAN Prediction Tool, etc.) there are currently are no validated diagnostic serum or urine biomarkers.
V. There are no curative therapies for IgAN. Supportive care with blood pressure management, use of renin-angiotensin system (RAS) blockers (ACEis or ARBs), and lifestyle modifications are the recommended initial interventions for IgAN treatment. Patients with proteinuria level of ≥1

g/day (or urine protein to creatinine ratio (UPCR) > 1.5 g/g) despite 3 to 6 months of initial treatment, are at high risk of progression to kidney failure. KDIGO guideline for the management of glomerular diseases strongly recommends proteinuria reduction < 1 g/day as a treatment goal for high-risk IgAN.

VI. Sparsentan (Filspari) is the first DEARA and the second drug approved for the treatment of IgAN. It follows IgAN-indicated budesonide (Tarpeyo). A nine-month course of glucocorticoids (e.g., prednisone, methylprednisolone) and/ or other immunosuppressants (e.g., hydroxychloroquine, mycophenolate) have been used for the treatment of high-risk IgAN. However, their use may be limited by other prognostic factors (e.g., eGFR > 30 mL/min/ 1.73 m^2), lack of strong clinical evidence, and considerations of treatment-related toxicities. Additionally, the KDIGO guideline recommends enrollment in a clinical trial for this patient population. Sparsentan (Filspari) may be considered a steroid-sparing alternative for the treatment of high-risk IgAN.

VII. The accelerated FDA approval for sparsentan (Filspari) was based on interim analysis of a randomized, double-blind, active-controlled phase 3 trial where patients were randomized 1:1 to either sparsentan (Filspari) 400 mg or irbesartan 300 mg once daily (PROTECT, N = 404). Adults with biopsy proven primary IgAN, proteinuria ≥ 1 g/day, eGFR ≥ 30 mL/min/1.73 m^2, and supportive therapy with an ACEi and/or ARB for ≥ 12 weeks were included in the study. Patients with secondary IgAN, documented history of immunosuppressant (including corticosteroids) use for ≥ 2 weeks within 3 months before screening, active CVD, hepatic or immune conditions were excluded. Baseline median proteinuria and mean eGFR in the sparsentan (Filspari) treatment arm were 1.8 g/day, and 56.9 mL/min/1.73m^2, respectively. Half (51.5%) of patients in the treatment arm had urinary protein excretion >1.75 g/day at baseline. The primary endpoint was met for the reported change in UPCR at week 36 versus baseline, which was -49.8% and -15% for sparsentan (Filspari) versus irbesartan (OR 0.6; 95% CI .5, 0.7; p <0.0001). Additionally, 55% patients in the treatment arm achieved proteinuria < 1 g/day at week 36. A supportive secondary endpoint: change in UPCR at week 94 was also reported to be statistically significant (52% versus 11%; p=0.0002).

VIII. During PROTECT clinical trial, a higher percentage of sparsentan (Filspari) treated patients reported treatment-emergent adverse event (TEAE) than irbesartan group (82.2% versus 73.3%), with dizziness (13%), peripheral edema (13%), hyperkalemia (10%), hypotension (10%), fatigue (8%), upper respiratory tract infections (6%), and acute kidney injury (4%) reported as the most common TEAE in the treatment arm. Kidney and urinary disorders were the most common severe AE reported in both arms leading to discontinuations (7.9% and 4.5% in the sparsentan (Filspari) and irbesartan arms, respectively).

IX. PROTECT clinical program consists of an ongoing trial, alluding to a short-term indication of efficacy. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial. Reduction in proteinuria < 1 g/day is an objective surrogate marker for IgAN. However, it falls shy of predicting long-term patient outcomes such as progression to ESRD, dialysis dependence and overall mortality in ESRD. The real-world utility of sparsentan (Filspari) is limited by exclusion of patients with cardiovascular disorders, anemia (Hb< 9 g/dL), and pre-existing CKD, which are considered major prognostic concerns related to renal impairment and are critical risk factors associated with mortality in CKD.

X. As of March 2023, the key pre-specified secondary endpoint (eGFR change over the time-points of 52 weeks, 104 weeks, and 110 weeks) remains unknown. An exploratory secondary endpoint

indicating complete remission (proteinuria < 0.3 g/day) at 36 weeks was not estimable, however, showed favorability toward sparsentan (Filspari) (10.3% versus 3.9%). Additional event-driven composite endpoint (confirmed 40% reduction in eGFR, kidney failure, or death) may be reported at the completion of PROTECT trial. An open-label extension (OLE) for the PROTECT clinical trial is currently ongoing along with two additional clinical trials to evaluate sparsentan (Filspari) for the treatment of focal segmental glomerulosclerosis (FSGS).

XI. Comparative efficacy of sparsentan (Filspari) versus IgAN-indicated budesonide (Tarpeyo) and other ACEi and/or ARB (e.g., lisinopril, enalapril, valsartan) remains unknown. For IgAN patients with high-risk of disease progression, IgAN-indicated budesonide (Tarpeyo) or other systemic corticosteroids (e.g., prednisone, methylprednisolone) have been used as treatment interventions. However, no corticosteroid, including budesonide (Tarpeyo), has been found to slow kidney function decline (reduce eGFR decline or progression to ESRD) in IgAN patients.

Investigational or Not Medically Necessary Uses

I. Sparsentan (Filspari) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below. There are currently ongoing trials in the setting of focal segmental glomerulosclerosis (FSGS). However, no data is available to support efficacy and safety of sparsentan (Filspari) for the treatment of FSGS:
   A. Secondary IgA nephropathy
   B. Newly diagnosed IgAN without high risk of disease progression
   C. Sparsentan (Filspari) used in combination with IgAN-indicated budesonide (Tarpeyo)
   D. Focal segmental glomerulosclerosis (FSGS)
   E. Chronic kidney disease (CKD) other than primary IgAN

II. During PROTECT clinical trial for sparsentan (Filspari), patients with a history of immunosuppressants, including corticosteroids, for more than 2 weeks within 3 months of screening were excluded. Efficacy and safety of sparsentan (Filspari) in combination with IgAN-indicated budesonide (Tarpeyo) and other systemic corticosteroids has not been evaluated. Due to the very high risk of adverse events, concurrent use of ACE inhibitors and ARB agents with sparsentan (Filspari) is contraindicated.

References

1. ClinicalTrials.gov. A Study of the Effect and Safety of Sparsentan in the Treatment of Patients With IgA Nephropathy (PROTECT). 2022 [updated 2022 October 4; cited 2022 October]; NCT03762850.
2. Travere Therapeutics. Travere Therapeutics Announces FDA Acceptance and Priority Review of New Drug Application for Sparsentan for the Treatment of IgA Nephropathy. February 2023. https://ir.travere.com/news-releases/news-release-details/travere-therapeutics-announces-fda-acceptance-and-priority
3. Filspari. Package Insert. Travere Therapeutics, San Diego CA; February 2023.
4. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases; J Int Soc Nephrol; 2021, 100 (45), S1-S276. https://kdigo.org/wp-content/uploads/2017/02/KDIGO-Glomerular-Diseases-Guideline-2021-English.pdf

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
Bbudesonide (Tarpeyo)	Primary IgA nephropathy; at high risk of progression

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2023

Policy Type: PA/SP Pharmacy Coverage Policy: UMP027

Description
AlphaNine SD, BeneFix, Ixinity, Mononine, and Rixubis are standard half-life factor IX products for the treatment and prevention of bleeding in patients with hemophilia B.

Length of Authorization
- Initial: 6 months (for on-demand and prophylaxis); 1 month (for perioperative)
- Renewal: 12 months (prophylaxis); 6 months (on-demand)

Quantity limits

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
AlphaNine SD, coagulation factor IX (human)	500, 1000, 1500 IU	**Control and prevention of bleeding episodes:** Up to 100 IU/kg; Repeat dose after 12 hours as needed for three to five days. Major hemorrhages may require treatment for up to ten days	**Control and prevention of bleeding episodes:** Up to the number of doses requested every 28 days
BeneFIX, coagulation factor IX (recombinant)	250, 500, 1000, 2000, 3000 IU	**Control and prevention of bleeding episodes and perioperative management*:** Up to 100 IU/dL; Consider repeat dose after 12 to 24 hours as needed for seven to ten days	**Control and prevention of bleeding episodes and perioperative management:** Up to the number of doses requested every 28 days
Ixinity, coagulation factor IX (recombinant)	250, 500, 1000 IU	**Control and prevention of bleeding episodes δ:** Up to 100 IU/dL, doses every 12 to 24 hours on days two through 14 until healing is achieved **Perioperative Management δ:** • *Minor*: Up to 80 IU/dL pre- and post-operative; Repeat every 24 hours on days one through five, depending on type of procedure • *Major*: Up to 80 IU/dL pre-op; Post-op: Up to 60 IU, dosed every 8 to 24 hours on days one through three, or up to 50 IU/dL dosed every 8 to 24 hours on days four through six, or up to 40 IU/dL dosed every 8 to 24 hours on days seven through 14	**Control and prevention of bleeding episodes:** Up to the number of doses requested every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
MonoNine, coagulation	500, 1000 IU	**Control and prevention of bleeding episodes and perioperative management:**	**Control and prevention of bleeding episodes and perioperative management:**

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
factor IX (human)		• Minor spontaneous hemorrhage prophylaxis: Up to 30 IU/kg for one dose. Repeat in 24 hours if necessary • Major trauma or surgery: Up to 75 IU/kg, dosed every 18 to 30 hours depending on T ½ and measured factor IX levels. Continue for up to ten days depending on nature of insult	Up to the number of doses requested every 28 days
Profilnine SD, factor IX complex	500, 1000, 1500 IU	**Control and prevention of bleeding episodes€:** Up to 50 IU/dL for a single dose. Daily infusions are generally required **Perioperative Management:** Up to 50 IU/kg every 16 to 24 hours for seven to ten days until healing is achieved.	**Control and prevention of bleeding episodes:** Up to the number of doses requested every 28 days **Perioperative Management:** Up to the number of doses requested every 28 days
Rixubis, coagulation factor IX (recombinant)	250, 500, 1000, 2000, 3000 IU	**Control and prevention of bleeding episodes ɣ:** Up to 100 IU/dL every 12 to 24 hours for seven to ten days, until bleeding stops and healing is achieved **Routine Prophylaxis:** • < 12 years: Up to 80 IU/kg twice weekly • ≥ 12 years: Up to 60 IU/kg twice weekly **Perioperative Management ɣ:** Up to 100 IU/dL every 8 to 24 hours for seven to ten days, until bleeding stops and healing is achieved	**Control and prevention of bleeding episodes:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • < 12 years: Up to 672 IU/kg every 28 days • ≥ 12 years: Up to 504 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested every 28 days

‡Allows for +5% to account for assay and vial availability

* One unit per kilogram body weight increases the circulating Factor IX level by 1% (IU/dL). Adult: Number of Factor IX IU required = body wt (kg) x Desired increase in Plasma Factor IX (%) x 1.3 IU/kg; Pediatric (<15 years): Number of Factor IX IU required = body wt (kg) x Desired increase in Plasma Factor IX (%) x 1.4 IU/kg

δ One IU per kg body weight increases the circulating activity of factor IX by 0.98 IU/dL

- Initial dose: required factor IX units (IU) = body weight (kg) x desired factor IX increase (% of normal IU/dL) x reciprocal of observed recovery (IU/kg per IU/dL)
- Maintenance dose: Depends upon the type of bleed or surgery, clinical response, and the severity of the underlying factor IX deficiency

€ One unit per kilogram body weight increases the circulating Factor IX level by 1% (IU/dL). Number of Factor IX IU required = body wt (kg) x Desired increase in Plasma Factor IX(percent) x 1.0 IU/kg

ɣ One IU per kilogram body weight increases the circulating activity of factor IX by 0.7 IU/dL for patients < 12 years of age and 0.9 IU/dL for patients ≥ 12 years of age. Initial dose = body wt (kg) x desired factor IX increase (percent of normal or IU/dL) x reciprocal of observed recovery (IU/kg per IU/dL)

Initial Evaluation

I. Standard half-life factor IX products may be considered medically necessary when the following criteria below are met:
   A. Member has a confirmed diagnosis of **hemophilia B (congenital factor IX deficiency)** the following are met:
      1. Treatment is prescribed by or in consultation with a hematologist; **AND**
      2. Use of standard half-life factor IX is planned for one of the following indications:
         i. On-demand treatment and control of bleeding episodes **AND** the number of factor IX units requested does not exceed those outlined in the Quantity Limits table above for routine prophylaxis; **OR**
         ii. Perioperative management of bleeding; **OR**
         iii. Routine prophylaxis to reduce the frequency of bleeding episodes when one of the following is met:
            a. Member has severe hemophilia B (defined as factor IX level of <1%); **OR**
            b. Member has had more than one documented episode of spontaneous bleeding; **AND**
      3. Documentation that inhibitor testing has been performed within the last 12 months AND if inhibitor titers are high (≥5 Bethesda units), there is a documented plan to address inhibitors; **AND**
      4. Dose and frequency does not exceed those outlined in the Quantity Limit Table above, unless documented clinical reasoning for higher dosing and/or frequency is supported by a half-life study to determine the appropriate dose and dosing interval

II. Standard half-life factor IX products are considered investigational when used for all other conditions.

Renewal Evaluation

I. For **on-demand treatment** and **routine prophylaxis**:
   i. Documentation of clinical benefit, including decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline; **AND**
   ii. Documentation that inhibitor testing has been performed within the last 12 months AND if inhibitor titers are high (≥5 Bethesda units), there is documented plan to address inhibitors; **AND**
   iii. *For **on-demand treatment only***, the dose and frequency is not greater than the routine prophylactic dose outlined in the Quantity Limit Table above

Supporting Evidence

I. Hemophilia B (factor IX deficiency) is an X-linked inherited coagulation factor deficiency that results in a lifelong bleeding disorder. The availability of factor replacement products has dramatically improved care for those with hemophilia B.

II. There are varying severities of hemophilia B depending on the level of factor produced by the patient. Hemophilia B is divided into the following categories based on severity:
    i. **Severe**: <1% factor activity (<0.01 IU/mL)
    ii. **Moderate**: Factor activity level ≥ 1% of normal and ≤ 5% of normal (≥ 0.01 and ≤ 0.05 IU/mL)
    iii. **Mild**: Factor activity level >5% of normal and < 40% of normal (> 0.05 and < 0.40 IU/mL

III. There are three general approaches to bleeding management in those with hemophilia B:
- Episodic ("on demand") treatment that is given at the time of clinically evident bleeding
- Perioperative management of bleeding for those undergoing elective surgery/procedures
- Routine prophylaxis is administered in the absence of bleeding to reduce bleeding and long-term complications of bleeding (e.g. arthropathy)

II. The current standard of care for hemophilia B is to replace the deficient coagulation factor either through episodic ("on demand") treatment given at the time of bleeding, or through continuous prophylaxis to prevent bleeding. Recombinant factor IX products are the treatment of choice for hemophilia B as recommended by The National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC).

III. MASAC recommends that prophylaxis be considered optimal therapy for individuals age one and older with severe hemophilia B. Therapy should be initiated early with the goal of keeping the trough factor IX level above 1% between doses.

IV. For individuals who have had more than one bleeding episode (e.g. two or more bleeds into a target joint, evidence of joint disease by physical exam or radiography), prophylaxis may be appropriate to prevent further morbidity, regardless of factor activity level.

V. The safety and efficacy of the standard half-life products were established based on open-label, non-randomized trails. All replacement products can produce satisfactory hemostasis.

Investigational or Not Medically Necessary Uses

There is no evidence to support the use of standard half-life factor IX products in any other condition.

References

1. AlphaNine SD [package insert]. Los Angeles, CA; Grifols Biologicals Inc.; January 2013.
2. BeneFIX [package insert]. Philadelphia, PA; Wyeth Biopharma; June 2017.
3. Ixinity [package insert]. Winnipeg, Manitoba, Canada. Cangene Corporation; December 2018.
4. Mononine [package insert]. Kankakee, IL; CSL Behring LLC; April 2016.
5. Rixubis [package insert]. Westlake Village, CA; Baxalta US Inc.; May 2018
1. National Hemophilia Foundation. Hemophilia A. Available from: https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-A. Accessed July 5, 2019.
2. National Hemophilia Foundation. MASAC Recommendations Concerning products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. Available from: https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations. Accessed July 5, 2019.
3. UpToDate, Inc. Hemophilia A and B: Routine management including prophylaxis. UpToDate [database online]. Last updated February 11, 2019.

Policy Implementation/Update:

Date Created	August 2019
Date Effective	August 2019
Last Updated	August 2019
Last Reviewed	08/2019

Action and Summary of Changes	Date
New policy created for standard half-life factor products	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP023

Description
Advate, Afstyla, Hemofil M, Kogenate FS, Koate DVI, Kovaltry, Novoeight, Nuwiq, Recombinate, and Xyntha are standard half-life factor VIII products for the treatment and prevention of bleeding in patients with hemophilia A.

Length of Authorization
- Initial: 6 months (for on-demand and prophylaxis); 1 month (for perioperative)
- Renewal: 12 months (for prophylaxis); 6 months (for on-demand)

Quantity limits

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
Advate, antihemophilic factor (recombinant)	250, 500, 1000, 1500, 2000, 3000, 4000 IU	**On-demand Treatment:** Up to 50 IU/kg every 8 to 24 hours until bleeding is resolved **Routine Prophylaxis:** • Up to 40 IU/kg every other day (3 to 4 times weekly) or every third day **Perioperative Management:** • *Minor* (e.g. tooth extraction): Up to 50 IU/kg within one hour before surgery; Repeat every 12 to 24 hours as needed until bleeding is resolved • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 60 IU/kg preoperative to achieve 100% activity; Repeat every 8 to 24 (every 6 to 24 hours for patients under the age of six) hours to keep factor VIII activity in desired range until healing is complete	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** Up to 672 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
Afstyla, antihemophilic factor	250, 500, 1000, 1500,	**On-demand Treatment:** Up to 50 IU/kg every 8 to 24 hours until bleeding is resolved	**On-demand Treatment:** Up to the number of doses requested every 28 days

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
(recombinant), single chain	2000, 2500, 3000 IU	**Routine Prophylaxis:** • ≥12 years: Up to 50 IU/kg two to three times per week • <12 years: Up to 50 IU/kg two to three times per week. More frequent or higher dosing may be required to account for the higher clearance in this age group. **Perioperative Management:** • *Minor* (e.g. tooth extraction): Up to 30 IU/kg every 24 hours for at least one day until healing is resolved • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 50 IU/kg every 8 to 24 hours until adequate wound healing, then continue therapy for at least another seven days	**Routine Prophylaxis:** • ≥12 years: Up to 630 IU/kg every 28 days • <12 years: Up to 630 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
Hemofil M, antihemophilic factor (human)	250, 500, 1000, 1700 IU	**On-demand Treatment** [δ]**:** Up to 100 IU/dL; Repeat every 8 to 24 hours until the bleeding threat is resolved **Perioperative Management** [δ]**:** • *Minor* (e.g. tooth extraction): A single infusion of up to 80 IU/dL plus oral antifibrinolytic therapy within one hour is sufficient in approximately 70% of cases • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 100 IU/dL pre- and post-operative; Repeat dose every 8 to 24 hours depending on state of healing	**On-demand Treatment:** Up to the number of doses requested every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
Koate DVI, antihemophilic factor (human)	250, 500, 1000 IU	**On-demand Treatment** [δ]**:** Up to 100 IU/dL every 8 to 12 hours until bleeding threat is resolved	**On-demand Treatment:** Up to the number of doses requested every 28 days

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
		Perioperative Management δ**:** For major surgical procedures, the factor VIII level should be raised to approximately 100% by giving a preoperative dose of 50 IU/kg. Repeat infusions may be necessary every 6 to 12 hours initially, and for a total of 10 to 14 days until healing is complete. The intensity of factor replacement therapy required depends on the type of surgery and postoperative regimen employed. For minor surgical procedures, less intensive treatment schedules may provide adequate homeostasis.	**Perioperative Management:** Up to the number of doses requested for 28 days
Kogenate FS, antihemophilic factor (recombinant), formulated with sucrose	250, 500, 1000, 2000, 3000 IU	**On-demand Treatment** δ**:** Up to 50 IU/kg every 8 to 12 hours until bleeding is resolved **Routine Prophylaxis:** • Adults: Up to 25 IU/kg three times per week • Children: Up to 25 IU/kg every other day **Perioperative Management** δ**:** • *Minor* (e.g. tooth extraction): Up to 30 IU/kg every 12 to 24 hours until bleeding is resolved • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 50 IU/kg preoperative to achieve 100% activity; Repeat every 6 to 12 hours to keep factor VIII activity in desired range until healing is complete	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • Adults: Up to 315 IU/kg every 28 days • Children: Up to 368 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
Kovaltry, antihemophilic factor (recombinant)	250, 500, 1000, 2000, 3000 IU	**On-demand Treatment** δ**:** Up to 100 IU/dL every 8 to 24 hours until bleeding is resolved **Routine Prophylaxis:** • ≥12 years: Up to 40 IU/kg two or three times per week	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • ≥12 years: Up to 504 IU/kg every 28 days

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
		• ≤ 12 years: Up to 50 IU/kg twice weekly, three times weekly, or every other day **Perioperative Management** δ**:** • *Minor* (e.g. tooth extraction): Up to 60 IU/dL every 24 hours until healing is achieved • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 100 IU/dL pre- and post-operative; Repeat every 8 to 24 hours until adequate wound healing is complete, then continue therapy for at least another seven days to maintain factor VIII activity of 30-60% (IU/dL)	• ≤12 years: Up to 735 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
Novoeight, antihemophilic factor (recombinant)	250, 500, 1000, 2000, 3000 IU	**On-demand Treatment** δ**:** Up to 100 IU/dL every 8 to 24 hours until resolution of bleed (approximately seven to ten days) **Routine Prophylaxis:** • ≥12 years: Up to 50 IU/kg three times per week or up to 40 IU/kg every other day • ≤ 12 years: Up to 60 IU/kg three times weekly or up to 50 IU/kg every other day **Perioperative Management** δ**:** • *Minor* (e.g. tooth extraction): Up to 60 IU/dL every 12 to 24 hours until bleeding is resolved • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 100 IU/dL pre- and post-operative; Repeat every 8 to 24 hours until adequate wound healing is complete, then continue therapy for at least another seven days to maintain factor VIII activity of 30-60% (IU/dL)	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • ≥12 years: Up to 630 IU/kg every 28 days • ≤12 years: Up to 756 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
Nuwiq, antihemophilic factor (recombinant)	250, 500, 1000, 1500, 2000, 2500, 3000, 4000 IU	**On-demand Treatment**δ**:** Up to 100 IU/dL every 8 to 24 hours until bleeding risk is resolved **Routine Prophylaxis:** • ≥12 years: Up to 40 IU/kg every other day • ≤ 12 years: Up to 50 IU/kg every other day or three times per week **Perioperative Management**δ**:** • *Minor* (e.g. tooth extraction): Up to 40 IU/dL every 12 to 24 hours until bleeding is resolved • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 100 IU/dL pre- and post-operative; Repeat every 8 to 24 hours until adequate wound healing, then continue therapy for at least another seven days to maintain factor VIII activity of 30-60% (IU/dL)	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • ≥12 years: Up to 588 IU/kg every 28 days • ≤12 years: Up to 735 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
Recombinate, antihemophilic factor (recombinant)	250, 500, 1000, 1500, 2000 IU	**On-demand Treatment**δ**:** Up to 100 IU/dL every 8 to 24 hours until bleeding threat is resolved **Perioperative Management**δ**:** • *Minor* (e.g. tooth extraction): Up to 80 IU/dL as a single infusion plus oral antifibrinolytic therapy within one hour is sufficient in approximately 70% of cases • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 100 IU/dL pre- and post-operative; Repeat every 8 to 24 hours depending on state of healing	**On-demand Treatment:** Up to the number of doses requested every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
Xyntha, antihemophilic	250, 500, 1000, 2000 IU	**On-demand Treatment**δ**:** Up to 100 IU/dL every 8 to 24 hours until bleeding threat is resolved	**On-demand Treatment:** Up to the number of doses requested every 28 days

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
factor (recombinant)		**Perioperative Management** δ**:** • *Minor* (e.g. tooth extraction): Up to 60 IU/dL for 3 to 4 days or until adequate hemostasis is achieved. For tooth extraction, a single infusion plus oral antifibrinolytic therapy within 1 hour may be sufficient • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 100 IU/dL pre- and post-operative; Repeat every 8 to 24 hours until threat is resolved, or in the case of surgery, until adequate local hemostasis and wound healing are achieved	**Perioperative Management:** Up to the number of doses requested for 28 days

‡Allows for +5% to account for assay and vial availability

δ Dose (IU/kg) = Desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL); *Expected Factor VIII rise (% of normal) = 2 x administered IU/body weight (kg)*

Initial Evaluation

I. Standard half-life factor VIII products may be considered medically necessary when the following criteria below are met:
   A. Member has a confirmed diagnosis of **hemophilia A (congenital factor VIII deficiency)** and the following are met:
      1. Treatment is prescribed by or in consultation with a hematologist; **AND**
      2. Use of standard half-life factor VIII is planned for one of the following indications:
         i. On-demand treatment and control of bleeding episodes **AND** the number of factor VIII units requested does not exceed those outlined in the Quantity Limits table above for routine prophylaxis; **OR**
         ii. Perioperative management of bleeding; **OR**
         iii. Routine prophylaxis to reduce the frequency of bleeding episodes when one of the following is met:
            a. Member has severe hemophilia A (defined as factor VIII level of <1%); **OR**
            b. Member has had more than one documented episode of spontaneous bleeding; **AND**
      3. Documentation that inhibitor testing has been performed within the last 12 months AND if inhibitor titers are high (≥5 Bethesda units), there is a documented plan to address inhibitors; **AND**

4. Dose and frequency does not exceed those outlined in the Quantity Limit Table above, unless documented clinical reasoning for higher dosing and/or frequency is supported by a half-life study to determine the appropriate dose and dosing interval

II. Standard half-life factor VIII products are considered investigational when used for all other conditions.

Renewal Evaluation

I. For **on-demand treatment** and **routine prophylaxis**:
   i. Documentation of clinical benefit, including decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline; **AND**
   ii. Documentation that inhibitor testing has been performed within the last 12 months AND if inhibitor titers are high (≥5 Bethesda units), there is documented plan to address inhibitors; **AND**
   iii. *For **on-demand treatment only**,* the dose and frequency is not greater than the routine prophylactic dose outlined in the Quantity Limit Table above

Supporting Evidence

I. Hemophilia A (factor VIII deficiency) is an X-linked inherited coagulation factor deficiency that results in a lifelong bleeding disorder. The availability of factor replacement products has dramatically improved care for those with hemophilia A.
II. There are varying severities of hemophilia A depending on the level of factor produced by the patient. Hemophilia A is divided into the following categories based on severity:
   i. **Severe**: <1% factor activity (<0.01 IU/mL)
   ii. **Moderate**: Factor activity level ≥ 1% of normal and ≤ 5% of normal (≥ 0.01 and ≤ 0.05 IU/mL)
   iii. **Mild**: Factor activity level >5% of normal and < 40% of normal (> 0.05 and < 0.40 IU/mL
III. There are three general approaches to bleeding management in those with hemophilia A:
   - Episodic ("on demand") treatment that is given at the time of clinically evident bleeding
   - Perioperative management of bleeding for those undergoing elective surgery/procedures
   - Routine prophylaxis is administered in the absence of bleeding to reduce bleeding and long-term complications of bleeding (e.g. arthropathy)
II. The current standard of care for hemophilia A is to replace the deficient coagulation factor either through episodic ("on demand") treatment given at the time of bleeding, or through continuous prophylaxis to prevent bleeding. Recombinant factor VIII products are the treatment of choice for hemophilia A as recommended by The National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC).
III. MASAC recommends that prophylaxis be considered optimal therapy for individuals age one and older with severe hemophilia A. Therapy should be initiated early with the goal of keeping the trough factor VIII level above 1% between doses.

IV. For individuals who have had more than one bleeding episode (e.g. two or more bleeds into a target joint, evidence of joint disease by physical exam or radiography), prophylaxis may be appropriate to prevent further morbidity, regardless of factor activity level.

V. The safety and efficacy of the standard half-life products were established based on open-label, non-randomized trails. All replacement products can produce satisfactory hemostasis.

Investigational or Not Medically Necessary Uses

There is no evidence to support the use of standard half-life factor VIII products in any other condition.

References

1. Advate [package insert]. Westlake Village, CA; Baxalta US Inc. May 2018.
2. Afstyla [package insert]. Kankakee, IL; CSL Behring, LLC; April 2017.
3. Hemofil M [package insert]. Westlake Village, CA; Baxalta US Inc. June 2018.
4. Koate DVI [package insert]. Research Triangle Park, NC; Grifols Therapeutics Inc.; August 2012.
5. Kogenate FS [package insert]. Whippany, NJ. Bayer HealthCare LLC; May 2016.
6. Novoeight [package insert]. Bagsvaerd, Denmark; Novo Nordisk; November 2018.
7. NUWIQ [package insert]. Elersvagen, Sweden; Octapharma AB; July 2017.
8. Recombinate [package insert]. Westlake Village, CA; Baxalta US Inc. June 2018.
9. Kovaltry [package insert]. Whippany, NJ; Bayer HealthCare LLC; March 2016
10. National Hemophilia Foundation. Hemophilia A. Available from: https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-A. Accessed July 5, 2019.
11. National Hemophilia Foundation. MASAC Recommendations Concerning products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. Available from: https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations. Accessed July 5, 2019.
12. UpToDate, Inc. Hemophilia A and B: Routine management including prophylaxis. UpToDate [database online]. Last updated February 11, 2019.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added 1500 strength of Nuwiq	02/2021
New policy created for standard half-life factor products	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP318

Description

Stiripentol (Diacomit) is an orally administered anticonvulsant with direct effects mediated through the GABAa receptor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
stiripentol (Diacomit)	Dravet Syndrome	250 mg capsules	180 capsules/30 days
		500 mg capsules	
		250 mg powder for oral suspension	180 packets/30 days
		500 mg powder for oral suspension	

Initial Evaluation

I. **Stiripentol (Diacomit)** may be considered medically necessary when the following criteria below are met:
   A. Member is 6 months of age or older; **AND**
      1. Member weighs at least 7 kg (15 lbs); **AND**
   B. Medication is prescribed by or in consultation with a neurologist; **AND**
   C. Medication will not be used as monotherapy (i.e., will be used in combination with another antiepileptic agent); **AND**
   D. A diagnosis of **Dravet Syndrome** when the following are met:
      i. Treatment with clobazam (Onfi) and valproate (Depakote) has been ineffective, contraindicated, or not tolerated; **AND**
      ii. Medication will be used in combination with clobazam (Onfi)

II. Stiripentol (Diacomit) is considered investigational when used for all other conditions, including but not limited to:
   A. Epileptic encephalopathies associated with SCN1A mutations
   B. Pharmacoresistant Focal Seizures
   C. Other non-FDA approved seizure disorder
   D. Primary Hyperoxaluria
   E. When used as monotherapy

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms [e.g., reduction in seizure frequency, seizure duration, incidence of ER visits or hospitalization due to seizure, etc.]; **AND**
IV. Medication will be used in combination with clobazam (Onfi)

Supporting Evidence

I. Dravet syndrome, previously known as severe myoclonic epilepsy in infancy, is a rare pediatric genetic epilepsy syndrome that typically presents within the first year of life (infancy) and is characterized by refractory epilepsy and neurodevelopmental problems. It can be difficult to diagnose, with common misdiagnoses including Lennox-Gastaut syndrome, cerebral palsy and vaccine encephalopathy. Because Dravet syndrome is generally treatment refractory, with high-touch care and monitoring required, stiripentol (Diacomit) must be prescribed by, or in consultation with a neurologist.
II. The use of stiripentol (Diacomit) has not been studied as monotherapy, and FDA labeling notes that there are no clinical data to support the use of stiripentol (Diacomit) as monotherapy. Therefore, if a member has a contraindication to therapy with clobazam, then another antiepileptic agent will be required to be used in combination with stiripentol (Diacomit).
III. Stiripentol (Diacomit) was studied in two Phase III, multicenter, randomized, placebo-controlled trials in 64 patients between the ages of three and 18 years who have been diagnosed with Dravet syndrome with previous inadequately controlled seizures on clobazam and valproate. Patients received stiripentol (Diacomit) as add-on therapy to on-going use of clobazam and valproate. The primary efficacy endpoint was responder rate, defined as a patient who experienced a >50% decrease in the frequency (per 30 days) of generalized clonic or tonic-clonic seizures, which was statistically significant for stiripentol (Diacomit) compared to placebo in both studies.
IV. The effectiveness of stiripentol (Diacomit) for patients aged six months to less than three years of age was extrapolated from the demonstration of effectiveness in patients aged three years to less than 18 years of age in the trials pivotal trials described above (supporting evidence I).
V. Although stiripentol (Diacomit) was studied in combination with both clobazam and valproate, the FDA indication is for the treatment of seizures associated with Dravet syndrome in patients taking clobazam. Pharmacokinetic data from the clinical trial revealed that the serum levels of both clobazam and its active component, norclobazam, were increased substantially with stiripentol (Diacomit), while the serum levels of valproate were unchanged. Because the relative contribution of efficacy of the increased levels of clobazam and norclobazam with stiripentol (Diacomit) treatment remains incompletely defined, along with concerns for long-term

teratogenicity and side effects of valproate, the FDA concluded that stiripentol (Diacomit) will be indicated in patients taking clobazam only.

VI. The NICE guidelines for Dravet syndrome recommend valproate as first-line therapy, then clobazam, and stiripentol (Diacomit) as adjunct first-line therapy. Cannabidiol (Epidiolex), in combination with clobazam, and fenfluramide (Fintepla) can also be considered as second-line add-on therapy. In addition to these guidelines, the international consensus on diagnosis and treatment of Dravet syndrome recommend first-line treatment with valproate, second-line with stiripentol (Diacomit), clobazam, or fenfluramine (Fintepla), and third-line with cannabidiol (Epidiolex).

Investigational or Not Medically Necessary Uses

I. Stiripentol (Diacomit) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Epileptic encephalopathies associated with SCN1A mutations
   B. Pharmacoresistant Focal Seizure
   C. Other non-FDA approved seizure disorder
   D. Primary hyperoxaluria
   E. When used as monotherapy
      i. Stiripentol (Diacomit) has not been studied as monotherapy in Dravet syndrome. Package label also notes lack of clinical data to support the use as monotherapy.

References

1. Diacomit [Prescribing Information]. Redwood City, CA: Biocodex, Beauvais, France. July 2022.
2. Center for Drug Evaluation and Research. Application Number 206709Orig1s000/207223Orig1s000 Summary Review. Summary Review for Regulatory Action: NDA206709/207223. Updated August 20, 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/206709Orig1s000,207223Orig1s000SumR.pdf
3. Stiripentol (Diacomit): For Severe Myoclonic Epilepsy in Infancy (Dravet Syndrome) [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2015 Apr. 3, RESULTS. Available from: https://www.ncbi.nlm.nih.gov/books/NBK349320/
4. Chiron C, Marchand MC, Tran A, Rey E, d'Athis P, Vincent J, et al. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group. Lancet. 2000 Nov 11;356(9242):1638–1642.
5. National Institute for Health and Care Excellence. Epilepsies in children, young people, and adults. Nice.org.uk. April 27, 2022. Accessed September 7, 2022.
6. National Institute for Health and Care Excellence. Fenfluramine for treating seizures associated with dravet syndrome. Nice.org.uk. July 8, 2022. Accessed September 7, 2022.
7. Wirrell EC, Hood V, Knupp KG, et al. International consensus on diagnosis and management of Dravet syndrome. Epilepsia. Published online May 12, 2022:epi.17274.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy

Policy Name	Disease state
cannabidiol (Epidiolex)	Lennox-Gastaut syndrome Dravet syndrome Tuberous Sclerosis Complex
fenfluramine (Fintepla)	Dravet syndrome Lennox-Gastaut syndrome

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated formatting of policy and quantity limit table; updated age requirement to 6 months and older; removed requirement for combination use with valproate from initial criteria; removed concomitant use with cannabidiol (Epidiolex) from E/I section	09/2022
Policy created	05/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP154

Split Fill Management*

Description

Sunitinib (Sutent) is an orally administered tyrosine kinase inhibitor targeting multiple receptors.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
sunitinib malate (generic Sutent)	12.5 mg capsule	Gastrointestinal stromal tumor Renal cell carcinoma, adjuvant following nephrectomy	28 capsules/42 days for all indications except neuroendocrine pancreatic tumor
	25 mg capsule		
	37.5 mg capsule	Renal cell carcinoma, advanced Neuroendocrine pancreatic tumor	28 capsules/28 days for pancreatic neuroendocrine tumor
	50 mg capsule		
sunitinib (Sutent)	12.5 mg capsule	Gastrointestinal stromal tumor Renal cell carcinoma, adjuvant following nephrectomy	28 capsules/42 days for all indications except neuroendocrine pancreatic tumor
	25 mg capsule		
	37.5 mg capsule	Renal cell carcinoma, advanced Neuroendocrine pancreatic tumor	28 capsules/28 days for pancreatic neuroendocrine tumor
	50 mg capsule		

Initial Evaluation

I. **Sunitinib (Sutent)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. Sunitinib (Sutent) will be used as monotherapy; **AND**
   D. The request is for generic sunitinib malate; **OR**
      1. The request is for brand Sutent and treatment with generic sunitinib malate is contraindicated or not tolerated; **AND**
   E. A diagnosis of one of the following:
      1. **Gastrointestinal stromal tumor (GIST)**; **AND**

i. Treatment with generic imatinib or brand imatinib (Gleevec) has been ineffective, contraindicated, or not tolerated; **OR**

2. **Pancreatic neuroendocrine tumor (pNET)**; **AND**
   i. The member has unresectable, locally advanced (stage III), or metastatic (stage IV) disease; **OR**
3. **Renal cell carcinoma (RCC); AND**
   i. Disease is advanced (stage III) or metastatic (stage IV)

II. Sunitinib (Sutent) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Adjuvant treatment for renal cell carcinoma

III. Sunitinib (Sutent) is considered investigational when used for all other conditions, including but not limited to:
   A. Angiosarcoma
   B. Breast cancer
   C. Colorectal cancer
   D. Central nervous system cancers
   E. Neuroendocrine tumors other than those of pancreatic origin
   F. Gastric cancer
   G. Lung cancer
   H. Soft tissue sarcoma
   I. Thyroid carcinoma
   J. Osteosarcoma
   K. Cholangiocarcinoma
   L. Adenoid cystic carcinoma

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. The request is for generic sunitinib malate; **OR**
   A. The request is for brand Sutent and treatment with generic sunitinib malate is contraindicated or not tolerated; **AND**
IV. Sunitinib (Sutent) will be used as monotherapy; **AND**
V. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread

Supporting Evidence

I. Sunitinib (Sutent) was evaluated for gastrointestinal stromal tumor (GIST) in a randomized, double-blind, placebo-controlled trial in adults that had previously progressed on imatinib (Gleevec) or were intolerant to therapy. Outcomes included time-to-tumor progression (TTP), progression-free survival (PFS), and objective response rate (ORR) and were statistically significant in favor of sunitinib (Sutent). At the time of disease progression, treatment was unblinded and those originally on placebo were allowed to crossover to open-label sunitinib (Sutent). At the final analysis overall survival (OS) was not statistically different between the treatment arms.

II. A second study of sunitinib (Sutent) for GIST was conducted as an open-label, single-arm trial in adults that had previously progressed on, or had intolerance to, imatinib (Gleevec). Five of the 55 subjects included had a partial response to therapy (9.1%, CI 3-20%).

III. For renal cell carcinoma (RCC), sunitinib (Sutent) was evaluated in a randomized trial versus IFN-a in treatment-naïve RCC. The outcomes evaluated were PFS and ORR, both of which were statistically significant in favor of sunitinib (Sutent).

IV. In the adjuvant treatment setting for RCC, sunitinib (Sutent) was evaluated in a randomized, double-blind, placebo-controlled trial adults with high risk of recurrence following nephrectomy. Subjects were required to have clear cell histology. Subjects were treated for nine cycles maximum. The primary outcome was disease-free survival (DFS) which was statistically significant in favor of sunitinib (Sutent). Overall survival was a secondary endpoint; however, data was not mature at time of analysis and the medication is associated with a significant safety profile.

V. For pancreatic neuroendocrine tumors (pNET), sunitinib (Sutent) was evaluated in a randomized, double-blind, placebo-controlled trial in adults with unresectable disease. The Independent Data Monitoring Committee was terminated early which may have led to an overestimate of the PFS. The outcomes of PFS and ORR were statistically significant in favor of sunitinib (Sutent); however, OS data was not mature at time of analysis. In a follow up analysis at five years a statistical significant different in OS was not demonstrated; however, this may have been confounded by crossover.

VI. Sunitinib has not been evaluated for safety and/or efficacy in pediatric patients. The dosing for sunitinib (Sutent) outside of pancreatic neuroendocrine tumors, is four weeks on two weeks off. A maximum of nine 6-week cycles of therapy for adjuvant RCC has been evaluated and FDA-approved for adjuvant RCC. This is approximately 13 months of therapy total.

Investigational or Not Medically Necessary Uses

I. Adjuvant treatment for renal cell carcinoma
   A. Following one year of treatment with sunitinib (Sutent), patients experienced a 1-year improvement in disease free survival compared to placebo; however, there was no improvement in overall survival. Sunitinib (Sutent) is associated with significant toxicity and patients experienced a decline in quality of life while on treatment compared to placebo. NCCN has listed adjuvant sunitinib (Sutent) as a Category 3 recommendation, as there is still no clear role for adjuvant systemic therapy in this setting. Observation or

clinical trials are still considered the standard of care given the lack of clinically meaningful supportive data for systemic therapy in the adjuvant setting.

II. Sunitinib (Sutent) has not been sufficiently studied for safety or efficacy and/or is currently being evaluated in clinical trials for the following indications:
    A. Angiosarcoma
    B. Breast cancer
    C. Colorectal cancer
    D. Central nervous system cancers
    E. Neuroendocrine tumors other than those of pancreatic origin
    F. Gastric cancer
    G. Lung cancer
    H. Soft tissue sarcoma
    I. Thyroid carcinoma
    J. Osteosarcoma
    K. Cholangiocarcinoma
    L. Adenoid cystic carcinoma

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Sutent [Prescribing Information]. New York, NY. Pfizer Labs. May 2019.
2. Demetri GD, Van oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet. 2006;368(9544):1329-38.
3. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007;356(2):115-24.
4. Ravaud A, Motzer RJ, Pandha HS, et al. Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy. N Engl J Med. 2016;375(23):2246-2254.
5. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med. 2011;364(6):501-13.
6. Faivre S, Niccoli P, Castellano D, et al. Sunitinib in pancreatic neuroendocrine tumors: updated progression-free survival and final overall survival from a phase III randomized study. Ann Oncol. 2017;28(2):339-343.

Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of trial and failure of generic sunitinib prior to use of branded Sutent. Addition of monotherapy requirements evaluated upon renewal. Updated initial approval duration from three months to six months.	09/2021
Prior authorization criteria transitioned to policy format. Addition of age edit, monotherapy requirements, and clarification of renal cell carcinoma uses.	11/2019
Review of adjuvant RCC setting	01/2018
Policy created	03/2012

Policy Type: PA/SP Pharmacy Coverage Policy: UMP246

Description

These agents target the JAK/STAT (janus associated kinase/signal transducer and activator of transcription) pathway that involves proteins, cytokines, and other inflammatory mediators that lead to immune activation and inflammation in chronic inflammatory disease states. The purpose of this policy is to ensure the appropriate use of these agents.

Length of Authorization

- Initial: Six months
- Renewal:
  i. Upadacitinib (Rinvoq) 45 mg XR tablet: No renewal
  ii. All other medications: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit*
abrocitinib (Cibinqo™)	Atopic Dermatitis (AD)	100 mg tablet	30 tablets/30 days
		200 mg tablet	
baricitinib (Olumiant®)	Rheumatoid Arthritis (RA)	1 mg tablet	30 tablets/30 days
		2 mg tablet	
	Alopecia areata§	2 mg tablet	N/A
		4 mg tablet	N/A
	COVID-19‡	4 mg tablet	N/A
deucravacitinib (Sotyktu™)	Plaque Psoriasis	6 mg tablet	30 tablets/30 days
upadacitinib (Rinvoq™)	Rheumatoid Arthritis (RA) Psoriatic arthritis (PsA) Ankylosing spondylitis (AS) Non-radiographic axial spondyloarthritis (nr-axSpA)	15 mg XR tablet	30 tablets/30 days
	Atopic Dermatitis (AD)	15 mg XR tablet	30 tablets/30 days
		30 mg XR tablet	
	Ulcerative Colitis (UC) Crohn's Disease (CD)	15 mg XR tablet	30 tablets/30 days
		30 mg XR tablet	
		45 mg XR tablet	28 tablets/28 days
tofacitinib (Xeljanz®)	Ankylosing spondylitis (AS) Rheumatoid Arthritis (RA) Psoriatic Arthritis (PsA)	5 mg tablet	60 tablets/30 days
		11mg XR tablet	30 tablets/30 days

	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	1mg/mL oral solution (240ml bottle)	Weight-based dosing: • 10 kg-20 kg: 1 bottle/30 days • 20 kg-40 kg: 1 bottle/30 days • Body weight ≥40 kg: 1 bottle/24 days
		5 mg tablet	Body weight ≥40 kg: 60 tablets/30 days**
	Ulcerative Colitis (UC)	5 mg tablet	60 tablets/30 days
		10mg tablet	
		11mg XR tablet	30 tablets/30 days
		22mg XR tablet	

**Lower doses may be used in renal and/or hepatic impairment, lymphopenia, neutropenia, anemia, strong CYP3A4 inhibitors (e.g., ketoconazole), strong CYP2C19 inhibitor(s) (e.g., fluconazole)*

§*Treatment for alopecia areata falls in the category of medications that are not covered under the prescription benefit. Drugs used for cosmetic purposes and/or to promote hair growth are excluded from coverage. Please reference the member handbook/certificate of coverage for further information.*

*** Dosing for PJIA is based on body weight. Patients with body weight greater than ≥40kg on the oral solution may be switched to Xeljanz 5 mg tablets.*

‡*Use of baricitinib (Olumiant) in the COVID-19 setting is indicated in hospitalized adults only. Per FDA label dosing is for 14 days or until hospital discharge, whichever occurs first. Review of coverage falls within the medical benefit and is excluded from the pharmacy benefit for this indication.*

Applicable to All Disease States and Treatment Options Listed Below

I. Contraindication to one preferred treatment option listed in the policies below does not exempt the requirement to try another required agent prior to biologic approval. For instance, in the rheumatoid arthritis requirements to follow, a contraindication to methotrexate but not to other available treatment options (sulfasalazine, hydroxychloroquine, leflunomide, etc.) would not satisfy criteria I(C)(1). In other words, a member would still need to try at least one of these other agents as clinically appropriate.

II. Approved treatments are not to be used in combination with other biologics or other non-biologic specialty medications used to treat autoimmune conditions. Use of tumor necrosis factor (TNF) blockers such as adalimumab in combination with other biologics, such as anakinra or abatacept, has demonstrated and increased risk of serious infection with insufficient evidence for added benefit. Per product labeling, use of JAK inhibitors with concomitant biologics or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended as there is insufficient data to support their use as dual therapy. Likewise, sufficient data is not currently available to support the safety and efficacy of apremilast use in combination with other agents listed in this policy.

Rheumatoid Arthritis

I. **Upadacitinib (Rinvoq) or tofacitinib (Xeljanz/Xeljanz XR)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   C. A diagnosis of **rheumatoid arthritis** when the following are met:

1. Treatment with an oral, non-biologic, non-specialty disease-modifying antirheumatic drug (DMARD) has been ineffective or not tolerated, or all are contraindicated (e.g., guidelines direct to methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide. Other examples include azathioprine and cyclosporine.); **AND**

D. Treatment with one or more tumor necrosis factor (TNF) blockers [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel) etc.] has been ineffective, not tolerated, or contraindicated.

II. **Baricitinib (Olumiant)** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(C) above are met; **AND**
   B. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), upadacitinib (Rinvoq), and tofacitinib (Xeljanz/Xeljanz XR) have been ineffective, contraindicated, or not tolerated.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat rheumatoid arthritis or another auto-immune condition (e.g., Otezla, Remicade, etc.).

Supporting Evidence

I. The agents listed above are approved for adult patients with rheumatoid arthritis (RA) that had an inadequate response or intolerance to TNF inhibitors based on safety and efficacy data from randomized-controlled trials.
II. The 2021 American College of Rheumatology (ACR) guidelines for rheumatoid arthritis address the use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), targeted-synthetic DMARDS (tsDMARDs) such as JAK inhibitors, and biologic DMARDS (bDMARDs) as TNF inhibitors and non-TNF inhibitors. A majority of recommendations are based on low or very low certainty of evidence.
    - The 2021 ACR guidelines strongly recommend the use of csDMARD monotherapy (methotrexate preferred) in patients who are DMARD-naïve with moderate-to-severe RA. Recommended csDMARDs include methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide. Despite moderate evidence in the SELECT-EARLY study noting higher efficacy of upadacitinib over methotrexate in DMARD-naïve patients with moderate-to-severe RA, there is limited long-term safety data to strongly recommend the use of tsDMARDs (e.g., JAK inhibitors) as first line therapy. Therefore, methotrexate monotherapy remains the preferred first-line therapy over tsDMARDs in DMARD-naïve patients based on established safety and efficacy.

Additionally, JAK inhibitors are not FDA approved for use in csDMARD-naïve patients.

- For patients who are DMARD-naïve with low disease activity, initial trial of hydroxychloroquine over other csDMARDs, and sulfasalazine over methotrexate is conditionally recommended.
- For DMARD-naive patients with moderate-to-severe disease activity, methotrexate monotherapy is conditionally recommended over methotrexate in combination with a TNF inhibitor due to low-certainty evidence with combination use. The recommendation is conditional because patients with poor prognostic factors may benefit from a faster onset of action and greater change of improvement with dual therapy.
- In DMARD-naive patients with moderate-to-severe disease activity, methotrexate monotherapy is strongly recommended over the addition of a non-TNF inhibitor or tsDMARD based additional risks of adding a biologic or tsDMARD and low-quality data evaluating superiority over methotrexate monotherapy.
- For patients with moderate-to-severe disease activity despite adequate trial of csDMARD monotherapy, a treat-to-target approach is strongly recommended and the addition of a bDMARD or tsDMARD is conditionally recommended as combination therapy may provide a more rapid treatment response. The recommendation was based on very low certainty of evidence.
- The guidelines conditionally recommend switching to a bDMARD or tsDMARD of a different class over switching to a bDMARD or tsDMARD belonging to the same class for patients taking a bDMARD or tsDMARD who are not at target, however the recommendation is based on very low-quality evidence supporting greater improvement in disease activity among patients switching therapy classes. There are no current recommendations for using a bDMARD over a tsDMARD, however patients and providers should engage in a shared decision-making approach based on the available safety data of JAK inhibitors.
- The 2021 ACR guidelines have additional recommendations for patient specific populations, including patients with co-morbid heart failure, lymphoproliferative disorder, Hepatitis B infection, nonalcoholic fatty liver disease (NAFLD), persistent hypogammaglobulinemia without infection, and populations with history of serious infection(s).

III. The 2019 European League Against Rheumatism (EULAR) guidelines follow similar recommendations to the 2021 ACR guidelines, and state that patients with highly active RA despite treatment with csDMARDs may receive a bDMARD or JAK inhibitor based on high level of evidence. Biologic DMARDS (TNF-inhibitors, IL-6 inhibitors, etc.) were previously recommended over JAK inhibitors, but newer data comparing JAK inhibitors to adalimumab failed to demonstrate clinically relevant endpoints favoring bDMARDs over JAK inhibitors.

IV. There are currently no head-to-head trials comparing the safety and efficacy of Xeljanz, Rinvoq, or Olumiant in patients with rheumatoid arthritis.

References

1. Fraenkel L, Bathon JM, England BR, et al. 2021 American college of rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res*. 2021;73(7):924-939.
2. Alten R, Mischkewitz M. 2021 ACR guideline reflects changes in RA treatment. *Nat Rev Rheumatol*. 2021;17(9):513-514. doi:10.1038/s41584-021-00667-2

3. Van Vollenhoven, R. et al. Efficacy and safety of upadacitinib monotherapy in methotrexate-naive patients with moderately-to-severely active rheumatoid arthritis (SELECT-EARLY): a multicenter, multi-country, randomized, double-blind, active-comparator-controlled trial. *Arthritis Rheumatol.* 72, 1607–1620 (2020)
4. UpToDate, Inc. General principles and overview of management of rheumatoid arthritis in adults . UpToDate [database online]. Waltham, MA. Last updated October 18, 2021. Available at: http://www.uptodate.com/home/index.html.
5. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis.* 2020;79:685-699.
6. Wang F, Sun L, Wang S, et al. Efficacy and Safety of Tofacitinib, Baricitinib, and Upadacitinib for Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. *Mayo Clin Proc*. 2020;95(7):1404-1419.

Polyarticular Juvenile Idiopathic Arthritis (PJIA)

Initial Evaluation

I. **Tofacitinib (Xeljanz)** may be considered medically necessary when the following criteria below are met:
   A. Member is 2 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   C. A diagnosis of **Polyarticular Juvenile Idiopathic Arthritis (PJIA)** when the following are met when the following are met:
      1. Treatment with at least one oral, non-biologic, non-specialty disease-modifying antirheumatic drug (DMARD) has been ineffective, contraindicated, or not tolerated. Guidelines direct to use of methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide. Other examples include azathioprine and cyclosporine; **AND**
   D. Treatment with one or more tumor necrosis factor (TNF) blockers [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel) etc.] has been ineffective, not tolerated, or contraindicated.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat polyarticular juvenile idiopathic arthritis or another auto-immune condition (e.g., Orencia, Actemra, Remicade, etc.)

Supporting Evidence

I. The above agent is approved for pediatric patients greater than two years of age with polyarticular juvenile idiopathic arthritis that had an inadequate response or intolerance to TNF inhibitors based on safety and efficacy data from randomized-controlled trials.
II. Juvenile idiopathic arthritis (JIA) is a grouping of inflammatory disorders that affect children. Polyarticular juvenile idiopathic arthritis (PJIA) is a subset of JIA, which is defined by the

presence arthritis in five or more joints during the first six months of illness. Other subsets of JIA include ERA, oligoarthritis (less than five joints affected), systemic juvenile idiopathic arthritis (SJIA; fever, rash, hepatic/splenic/lymphatic involvement), and psoriatic arthritis (psoriasis and dactylitis). While these are distinct disease states, their pathogenesis and presentation are similar so there is significant overlap in effective treatments.

III. The 2019 ACR JIA guidelines for non-systemic polyarthritis (PJIA) strongly recommend initial therapy with a DMARD for all patients with JIA and active polyarthritis; methotrexate has the strongest evidence, but sulfasalazine and leflunomide can also be used. Adjunctive therapy with NSAIDs and oral or intra-articular glucocorticoids is common. Regardless of disease activity, initial therapy with a DMARD is recommended over a biologic, though there may be certain situations where a biologic as initial therapy is preferred (i.e., high-risk joints such as cervical spine, wrist, or hip involved). ACR notes that while initial treatment with biologics was studied in the TREAT-JIA and ACUTE-JIA studies, results were not deemed conclusive enough to make recommendations for biologics as initial therapy at this time. For patients with continued moderate to high disease activity, the guidelines recommend adding a TNF inhibitor, abatacept, or tocilizumab as second-line. The ACR guidelines make a conditional recommendation for switching to non-TNF inhibitor biologics (tocilizumab and abatacept) in patients receiving a TNF inhibitor with continued moderate or high disease activity. It is noted that a second TNF inhibitor may be appropriate for patients who had a good initial response to the first TNF inhibitor but had secondary failure due to suspected drug antibodies developing, and that this conditional recommendation stems from data in adult rheumatoid arthritis patients. Juvenile psoriatic arthritis follows the same treatment paradigm.

IV. A phase 3 double-blind, randomized, placebo-controlled withdrawal study (PROPEL) evaluated the efficacy and safety of tofacitinib (Xeljanz) in patients aged 2-17 years old with active PJIA and who had inadequate response to at least one DMARD or biologic DMARD. The primary endpoint evaluated the occurrence of disease flare at week 44 and was found to be statistically significantly lower in tofacitinib (Xeljanz) group vs the placebo group (29.2 % vs 59.2%, p-value=0.0031). The secondary endpoint found improvements from baseline in questionnaires JIA ACR 30/50/70 and Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI) in tofacitinib vs placebo. Some limitations to the study include potential bias in the open label arm of the study, and the study is unpublished with limited information such as the population of patents currently on DMARD or oral glucocorticoid.

V. Dosing for PJIA is based on body weight. Patients with body weight greater than $\geq$40kg on the oral solution may be switched to Xeljanz 5 mg tablets.

References

1. UpToDate, Inc. Spondyloarthritis in children. UpToDate [database online]. Waltham, MA. Last updated December 4, 2020. Available at uptodate.com. Accessed February 4, 2022.
2. Tofacitinib (Xeljanz/Xeljanz XR) [Prescribing Information]. New York, NY; Pfizer Inc., Updated January 2022.
3. Ringold S, Angeles-han ST, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis. Arthritis Care Res (Hoboken). 2019.
4. UpToDate, Inc. Polyarticular juvenile idiopathic arthritis: treatment. UpToDate [database online]. Waltham, MA. Last updated October 19, 2020. Available at: http://www.uptodate.com/home/index.html. Last accessed November 22 ,2021.
5. Brunner H, Ting T, el al. Tofacitinib in treatment of Polyarticular-course Juvenile idiopathic Arthritis: Results of a Phase 3 Randomized Double-blind Placebo withdrawal Study. ACR 2019. Abstract number: L22

6. Safety and Tolerability of Tofacitinib for Treatment of Polyarticular Course Juvenile Idiopathic Arthritis. 2020 [PROPEL Study] (NCT02592434)

Psoriatic Arthritis

Initial Evaluation

I. **Tofacitinib (Xeljanz/Xeljanz XR) or upadacitinib (Rinvoq)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist or dermatologist; **AND**
   C. A diagnosis of active **psoriatic arthritis** when the following are met:
      1. Treatment with non-biologic, non-specialty oral small molecules (OSMs) such as methotrexate, leflunomide, sulfasalazine, or cyclosporine has been ineffective, contraindicated, or not tolerated; **OR**
      2. Presence of active, severe disease as indicated by provider assessment and the presence of at least one of the following:
         i. Erosive disease
         ii. Elevated CRP or ESR
         iii. Long-term damage interfering with function (e.g., joint deformities, vision loss)
         iv. Major impairment of quality of life due to high disease activity at many sites (including dactylitis, enthesitis) or functionally limiting arthritis at a few sites; **AND**
   D. Treatment with one or more tumor necrosis factor (TNF) blockers [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel) etc.] has been ineffective, not tolerated, or contraindicated.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat psoriatic arthritis or another auto-immune condition (e.g., Otezla, Olumiant, etc.)

Supporting Evidence

I. Tofacitinib (Xeljanz/Xeljanz XR) and upadacitinib (Rinvoq) are approved for adult patients with psoriatic arthritis (PsA) that had an inadequate response or intolerance to tumor necrosis factor (TNF) inhibitors based on safety and efficacy data from randomized-controlled trials.

II. The 2018 ACR guidelines for psoriatic arthritis make a conditional recommendation for starting a TNF inhibitor over an OSM as a first-line option for patients who are treatment-naïve with active psoriatic arthritis. This recommendation is based on low- to very-low quality of evidence. Many of the studies in which greater benefit was seen in terms of disease severity or radiographic progression compared methotrexate to TNF inhibitors, however, most patients included in these groups were not truly treatment naïve to OSM medications. Guidelines note that OSM can be used first-line in naïve patients who do not have severe PsA, severe PsO, prefers oral therapy, or has contraindications to TNF inhibitors. In patients who continue to have active disease despite OSM treatment, it is recommended to switch to a TNF inhibitor rather than trying a different OSM.

III. A systematic review of RCTs published in 2015 examined differences in terms of ACR20 response with biologic versus synthetic DMARDs. A statistically significant benefit was not demonstrated with methotrexate, cyclosporine, or sulfasalazine. Leflunomide did demonstrate a statistically significant benefit, though the magnitude of benefit was lower than all of the biologic DMARDs analyzed. There are many limitations to this review, such as a large proportion of trials/data that only included a small number of patients (less than 100). A recent study compared the TNF inhibitor etanercept to methotrexate monotherapy in patients naïve to both biologics and methotrexate. Patients treated with etanercept were statistically more likely to achieve ACR20 response at week 24 compared to the methotrexate monotherapy group (difference 9.2%, 95% CI 1.0 to 17.3, p = 0.029).

IV. The 2018 ACR guidelines for psoriatic arthritis also conditionally recommend for use of a TNF inhibitor biologics over IL-17 inhibitors (ixekizumab, secukinumab) or IL-12/23 inhibitors (ustekinumab). As of January 2022, guidelines have not been updated to place upadacitinib in the PsA treatment algorithm.

References

1. Tofacitinib (Xeljanz/Xeljanz XR) [Prescribing Information]. New York, NY; Pfizer Inc., Updated January 2022.
2. Upadacitinib (Rinvoq) [Prescribing Information]. North Chicago, IL; AbbVie. Updated January 2022.
3. Singh JA, Guyatt G, Ogdie A, et al. Special Article: 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. *Arthritis Rheumatol*. 2019;71(1):5-32.
4. Kingsley GH, Scott DL. Assessing the effectiveness of synthetic and biologic disease-modifying antirheumatic drugs in psoriatic arthritis - a systematic review. Psoriasis (Auckl). 2015;5:71-81.
5. UpToDate, Inc. Treatment of psoriatic arthritis. UpToDate [database online]. Waltham, MA. Last updated November 20, 2020. Available at: http://www.uptodate.com/home/index.html.

Ankylosing Spondylitis

Initial Evaluation

I. **Tofacitinib (Xeljanz) or upadacitinib (Rinvoq)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   C. A diagnosis of **ankylosing spondylitis** when the following are met:
      1. High disease activity as indicated by BASDAI score of at least 4 or ASDAS score of at least 2.1; **AND**

2. Treatment with at least two different NSAIDs (e.g., indomethacin, meloxicam, celecoxib, naproxen, nabumetone, etc.) over four weeks has been ineffective, contraindicated, or not tolerated; **AND**
3. Disease manifested as axial disease; **OR**
4. Disease manifested as peripheral arthritis; **AND**

D. Treatment with one or more tumor necrosis factor (TNF) blockers [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel) etc.] has been ineffective, not tolerated, or contraindicated.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat ankylosing spondylitis or another auto-immune condition (e.g., Otezla, Olumiant, infliximab, etc.)

Supporting Evidence

I. Tofacitinib (Xeljanz) and upadacitinib (Rinvoq) are approved for adult patients with active ankylosing spondylitis (AS or ax-SpA) that had an inadequate response or intolerance to TNF inhibitors based on safety and efficacy data from randomized-controlled trials.
II. The 2019 ACR/SAA/SPARTAN guidelines on the treatment of ankylosing spondylitis strongly recommend the use of NSAIDs as first-line treatment (with 70-80% responding). Recommendations against the use of non-biologic DMARDs are made for patients with active ankylosing spondylitis despite NSAID treatment. Some benefit has been seen in patients with peripheral arthritis, thus treatment with sulfasalazine or methotrexate may be considered in patients with predominantly peripheral disease; however, evidence is based on older RCTs with very low quality of evidence. For those patients with inadequate response despite continuous NSAID treatment, the ACR strongly recommends use of TNF inhibitors over no treatment with TNF inhibitors. Moreover, the panel conditionally recommends treatment with secukinumab or ixekizumab over sulfasalazine, methotrexate, or tofacitinib. In patients with primary nonresponse, defined as absence of improvement after 3- 6 months of treatment initiation, secukinumab or ixekizumab is conditionally recommended over switching to a different TNF inhibitor. In patients with secondary nonresponse to TNF inhibitors, the guidelines conditionally recommend treatment with a different TNF inhibitor over treatment with a non-TNF inhibitor biologic. The guidelines have not been updated with regard to place in therapy for upadacitinib as of November 2022.
III. The 2022 ASAS/EULAR guidelines for the treatment of axial spondyloarthritis (axSpA) reference the use of JAK inhibitors in the treatment algorithm. The term axial spondyloarthritis (axSpA), encompasses both active ankylosing spondylitis (or radiographic AS) and nr-axSpA as one entity

part of the same chronic inflammatory musculoskeletal spectrum with similar clinical presentations, comorbidities, disease burden, and treatment response. ASAS/EULAR recommends patients try and fail at least 2 NSAIDs over 4 weeks as first line therapy and treat local musculoskeletal inflammation with glucocorticoid injection; sulfasalazine may be considered in patients with peripheral symptoms, however use of conventional non-biologic DMARDS (e.g. sulfasalazine, leflunomide, methotrexate, etc.) is not recommended in axial disease. In contrast to ACR/SAA/SPARTAN, ASAS/EULAR guidelines highly recommend treatment with a TNF inhibitor, IL-17 inhibitor, or JAK inhibitor for patients with high disease activity, defined by a BASDAI of at least 4 or an ASDAS of at least 2.1, despite conventional treatment with NSAIDS. Starting with a TNF inhibitor or IL-17 inhibitor is preferred clinically, given long term data for use of JAK inhibitors in axSpA is still missing. There is no specific treatment algorithm after primary non-response to biologic (TNF inhibitor or IL-17 inhibitor) or JAK inhibitor therapy. In absence of data showing superiority in the treatment sequence, switching to another biologic DMARD (TNF inhibitor or IL-17 inhibitor) or a JAK inhibitor may be considered.

IV. Although specific JAK inhibitors were not referenced in the ASAS/EULAR guideline, precautions for cardiovascular risk, malignancy, and thromboembolic events should be considered in patients starting JAK inhibitors. It is unclear whether the increased risk of cardiovascular events and malignancies is specific to a diagnosis of RA, reflective of a JAK inhibitor class effect, or specific to tofacitinib. Until more data become available, ASAS/EULAR advises against starting JAK inhibitors in specific populations: patients above 50 years of age with one or more cardiovascular risk factor and patients older than 65 years of age.

References

1. Tofacitinib (Xeljanz/Xeljanz XR) [Prescribing Information]. New York, NY; Pfizer Inc., Updated January 2022.
2. Upadacitinib (Rinvoq) [Prescribing Information]. North Chicago, IL; AbbVie. Updated October 2022.
3. Ward, M.M., Deodhar, A., Gensler, L.S, et al. 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Rheumatol*, 71: 1599-1613.
4. Ramiro S, Nikiphorou E, Sepriano A, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. *Ann Rheum Dis*. Published online October 21, 2022:ard-2022-223296.
5. UpToDate, Inc. Clinical manifestations of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults. UpToDate [database online]. Waltham, MA. Last updated November 2, 2022. Available at: http://www.uptodate.com/home/index.html.
6. UpToDate, Inc. Treatment of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondloarthritis) in adults. UpToDate [database online]. Waltham, MA. Last updated August 24, 2022. Available at: http://www.uptodate.com/home/index.html.
7. UpToDate, Inc. Treatment of peripheral spondyloarthritis. UpToDate [database online]. Waltham, MA. Last updated March 17, 2022. Available at: http://www.uptodate.com/home/index.html.

Non-radiographic Axial Spondyloarthritis

Initial Evaluation

I. **Upadacitinib (Rinvoq)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist; **AND**

C. A diagnosis of **non-radiographic axial spondyloarthritis** when the following are met:
    1. High disease activity as indicated by BASDAI score of at least 4 or ASDAS score of at least 2.1; **AND**
    2. Treatment with at least two different NSAIDs (e.g., indomethacin, meloxicam, celecoxib, naproxen, nabumetone, etc.) over four weeks has been ineffective, contraindicated, or not tolerated; **AND**
    3. Disease manifested as axial disease; **OR**
    4. Disease manifested as peripheral arthritis; **AND**
D. Treatment with one or more tumor necrosis factor (TNF) blockers [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel) etc.] has been ineffective, not tolerated, or contraindicated

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat non-radiographic axial spondyloarthritis or another auto-immune condition (e.g., Otezla, Olumiant, Infliximab, etc.)

Supporting Evidence

I. Upadacitinib (Rinvoq) is the only JAK inhibitor that is FDA-approved for adult patients with active non-radiographic axial spondyloarthritis (nr-axSpA) that had an inadequate response or intolerance to TNF inhibitors based on safety and efficacy data from randomized-controlled trials.
II. Currently, upadacitinib, certolizumab pegol, ixekizumab, and secukinumab are the only FDA approved agent for adults with nr-axSpA. Other TNF inhibitors are approved in Europe for this indication, have demonstrated efficacy in RCTs, and are utilized frequently in clinical practice. A study of 192 patients taking adalimumab demonstrated significant improvement compared to placebo in ASAS40 response by week 12 in patients with non-radiographic disease (36% vs 15%, $p < 0.001$). Likewise, etanercept and golimumab have also been approved by the European Medicines Agency, and the 2022 ASAS/EULAR guidelines note that efficacy in regard to musculoskeletal signs and symptoms appears comparable based off indirect comparison.
III. Per 2019 ACR/SAA/SPARTAN guidelines for AS and nr-axSpA, the panel strongly recommends treatment with TNF inhibitors over no treatment with TNF inhibitors. Moreover, the panel conditionally recommends treatment with TNF inhibitors over treatment with secukinumab or ixekizumab, and conditionally recommends treatment with secukinumab or ixekizumab over tofacitinib. In patients with primary nonresponse to the first TNF inhibitor, the panel conditionally recommends switching to secukinumab or ixekizumab over switching to a different

TNF inhibitor. As of November 2022, guidelines have not been updated with regard to place in therapy for upadacitinib for nr-axSpA.

IV. The 2022 ASAS/EULAR guidelines for the treatment of axial spondyloarthritis (axSpA) reference the use of JAK inhibitors in the treatment algorithm. The term axial spondyloarthritis (axSpA), encompasses both active ankylosing spondylitis (or radiographic AS) and nr-axSpA as one entity part of the same chronic inflammatory musculoskeletal spectrum with similar clinical presentations, comorbidities, disease burden, and treatment response. ASAS/EULAR recommends patients try and fail at least 2 NSAIDs over 4 weeks as first line therapy and treat local musculoskeletal inflammation with glucocorticoid injection; sulfasalazine may be considered in patients with peripheral symptoms, however use of conventional non-biologic DMARDS (e.g. sulfasalazine, leflunomide, methotrexate, etc.) is not recommended in axial disease. In contrast to ACR/SAA/SPARTAN, ASAS/EULAR guidelines highly recommend treatment with a TNF inhibitor, IL-17 inhibitor, or JAK inhibitor for patients with high disease activity, defined by a BASDAI of at least 4 or an ASDAS of at least 2.1, despite conventional treatment with NSAIDS. Starting with a TNF inhibitor or IL-17 inhibitor is preferred clinically, given long term data for use of JAK inhibitors in axSpA is still missing. There is no specific treatment algorithm after primary non-response to biologic (TNF inhibitor or IL-17 inhibitor) or JAK inhibitor therapy. In absence of data showing superiority in the treatment sequence, switching to another biologic DMARD (TNF inhibitor or IL-17 inhibitor) or a JAK inhibitor may be considered.

V. Although specific JAK inhibitors were not referenced in the ASAS/EULAR guideline, precautions for cardiovascular risk, malignancy, and thromboembolic events should be considered in patients starting JAK inhibitors. It is unclear whether the increased risk of cardiovascular events and malignancies is specific to a diagnosis of RA, reflective of a JAK inhibitor class effect, or specific to tofacitinib. Until more data become available, ASAS/EULAR advises against starting JAK inhibitors in specific populations: patients above 50 years of age with one or more cardiovascular risk factor and patients older than 65 years of age.

References

1. Upadacitinib (Rinvoq) [Prescribing Information]. North Chicago, IL; AbbVie. Updated October 2022.
2. Deodhar A, Gensler LS, Kay J, et al. A 52-week randomized placebo-controlled trial of certolizumab pegol in non-radiographic axial spondyloarthritis. *Arthritis Rheumatol.* 2019.
3. Sieper J, Van der heijde D, Dougados M, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). *Ann Rheum Dis.* 2013;72(6):815-822.
4. Deodhar A, van der Heijde D, Gensler LS, Kim TH et al. Ixekizumab for patients with non-radiographic axial spondyloarthritis (COAST-X): a randomised, placebo-controlled trial. *Lancet* 2020;395(10217):53-64.
5. Ward, M.M., Deodhar, A., Gensler, L.S, et al. 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Rheumatol*, 71: 1599-1613.
6. Ramiro S, Nikiphorou E, Sepriano A, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. *Ann Rheum Dis*. Published online October 21, 2022:ard-2022-223296.
7. UpToDate, Inc. Clinical manifestations of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults. UpToDate [database online]. Waltham, MA. Last updated November 2, 2022. Available at: http://www.uptodate.com/home/index.html.
8. UpToDate, Inc. Treatment of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondloarthritis) in adults. UpToDate [database online]. Waltham, MA. Last updated August 24, 2022. Available at: http://www.uptodate.com/home/index.html.
9. UpToDate, Inc. Treatment of peripheral spondyloarthritis. UpToDate [database online]. Waltham, MA. Last updated March 17, 2022. Available at: http://www.uptodate.com/home/index.html.

Plaque Psoriasis

Initial Evaluation

I. **Deucravacitinib (Sotyktu)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with a dermatologist; **AND**
   C. Not used in combination with other biologics or other non-biologic specialty medications [e.g., apremilast [Otezla], adalimumab (Humira), risankizumab (Skyrizi)] used to treat autoimmune conditions; **AND**
   D. A diagnosis of **moderate-to severe-plaque psoriasis** when the following are met:
      1. Chronic disease (greater than 6 months); **AND**
      2. At least 10% body surface area is involved or involves areas of the face, ears, hands, feet or genitalia; **AND**
      3. Treatment with the following has been ineffective or not tolerated, or all are contraindicated;
         i. Phototherapy (UVB or PUVA); **OR**
         ii. At least one non-biologic, non-specialty DMARD (e.g., methotrexate, cyclosporine, acitretin, etc.); **AND**
         iii. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), secukinumab (Cosentyx), ustekinumab (Stelara), risankizumab (Skyrizi), apremilast (Otezla), and guselkumab (Tremfya) have been ineffective, contraindicated, or not tolerated.

II. Deucravacitinib (Sotyktu) is considered investigational when used for all other conditions, including but not limited to:
   A. Psoriasis in pediatric and adolescent patients
   B. Psoriatic arthritis
   C. Lupus erythematosus
   D. Inflammatory bowel disease

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat plaque psoriasis or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, Rinvoq, etc.).

Supporting Evidence

I. Deucravacitinib (Sotyktu) has been evaluated for the treatment of moderate-to-severe plaque psoriasis in adult patients at a dose of 6 mg daily. Guidelines define moderate psoriasis to be 3-10% of the body surface area (BSA) and severe is defined as greater than or equal to 10% BSA involvement. Psoriasis can be considered severe irrespective of BSA when it occurs in certain locations (e.g., hands, feet, face, genital area). Guidelines provide a Grade A recommendation for use of biologics and apremilast (Otezla) for the treatment of moderate-to-severe plaque psoriasis. Guidelines do not point to a specific agent or class when initiating treatment with a biologic or other oral specialty therapy. Flares of psoriasis may be transient and may not require systemic therapy; thus, disease duration of six months is required to determine medical necessity for systemic therapy.

II. Guidelines indicate that the majority of patients are capable of adequately controlling disease solely with topical medications or phototherapy. Phototherapy is recognized as a beneficial therapy for controlled plaque psoriasis, and is a cost-effective treatment strategy. Additionally, oral immunomodulatory medications (e.g., methotrexate, cyclosporine, acitretin) are cost-effective therapies with a well-known safety profile for the treatment of plaque psoriasis. For moderate-to-severe disease, where a JAK inhibitor or biologics are warranted, deucravacitinib (Sotyktu) is one of many options. However, it would not be indicated for mild psoriasis given that patients are better managed from a safety perspective on well-established therapies (e.g., topical agents, phototherapy, conventional DMARDS, apremilast [Otezla]). Although deucravacitinib (Sotyktu) has been evaluated and showed to be superior to apremilast (Otezla) in clinical trials for patients with moderate to severe psoriasis, regarding the extent of patients able to achieve outcomes such as PASI75 and PGA0/1, results cannot be readily applied to patients with mild psoriasis. Given the largely unknown safety profile of deucravacitinib (Sotyktu) overall, the risk-to-benefit ratio of using deucravacitinib (Sotyktu) in mild disease is unknown. Alternatively, established therapies should continue to be the mainstay of therapy for these patients.

III. In terms of efficacy, deucravacitinib (Sotyktu) has showed superiority only to apremilast (Otezla) in clinical trials; however, it joins many other efficacious therapies that have well-established safety profiles (e.g., TNF-a inhibitors, IL-17, IL23 therapies). In clinical trials, 50-60% patients on deucravacitinib (Sotyktu) met PASI75. When indirectly comparing, it is not likely superior to the majority of established biologics for psoriasis. Additionally, within the last few years, there has been great improvement in outcomes patients are able to achieve with newer, targeted therapies for psoriasis. Notably, the potential for patients to reach PASI90 and PASI100 within a year of treatment has greatly increased, leading to a rethinking of primary and secondary endpoints evaluated as the standard. For example, 40-60% of patients treated with IL-17 and IL-23 therapies met PASI100 at one year in recent clinical trials. Given established safety profiles, known efficacy, and cost-effectiveness, trial of preferred psoriasis therapies such as biologics as listed in the criteria, are required for trial and failure or intolerance, unless contraindicated.

IV. In subgroup analyses in deucravacitinib (Sotyktu) trials patients with a BMI of 35 kg/m2 or greater may not as readily respond to deucravacitinib (Sotyktu) compared to patients under 35 kg/m2 BMI with otherwise similar characteristics; however, there is no evidence for safety and efficacy for up dosing beyond 6 mg. There is largely unknown safety profile for this new JAK therapy, and the full extent of the safety profile is likely to be realized from real-world data

when duration of use is extended and used in larger patient populations. Until data are available to confirm safety and efficacy of more than 6 mg per day, quantity exceptions will not be allowed.

Investigational or Not Medically Necessary Uses

I. Deucravacitinib (Sotyktu) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Psoriasis in pediatric and adolescent patients
   B. Psoriatic arthritis
   C. Lupus erythematosus
   D. Inflammatory bowel disease

References

1. Deucravacitinib product dossier. Bristol Myers Squibb. April 18, 2022.
2. Menter A, Gelfand JM, Connor C, et al. Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies. Journal of the American Academy of Dermatology. 2020;82(6):1445-1486.
3. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. Journal of the American Academy of Dermatology. 2019;80(4):1029-1072.

Ulcerative Colitis

Initial Evaluation

I. **Tofacitinib (Xeljanz/Xeljanz XR) or upadacitinib (Rinvoq)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a gastroenterologist; **AND**
   C. Diagnosis of **moderate to severe ulcerative colitis; AND**
   D. Provider attestation or clinical documentation of at least one of the following:
      1. Treatment with systemic corticosteroids (e.g., prednisone, budesonide) has been ineffective, contraindicated, or not tolerated; **OR**
      2. Treatment with an immunomodulator (e.g., azathioprine, 6-mercaptopurine) has been ineffective, contraindicated, or not tolerated; **AND**
   E. Treatment with one or more tumor necrosis factor (TNF) blockers [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], infliximab (Remicade) etc.] has been ineffective, not tolerated, or contraindicated.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**

IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat ulcerative colitis or another auto-immune condition (e.g., Remicade, Entyvio, Cimzia, etc.)

Supporting Evidence

I. Tofacitinib (Xeljanz/Xeljanz XR) and upadacitinib (Rinvoq) are FDA approved in the treatment of moderate to severe ulcerative colitis (UC) in adult patients over eighteen years of age that had an inadequate response or intolerance to one or more TNF inhibitors based on safety and efficacy data from randomized-controlled trials. As of May 2021, only adalimumab (Humira) has been FDA approved in moderate to severe ulcerative colitis in pediatric patients aged 5 years and older.

II. Tofacitinib (Xeljanz), adalimumab (Humira), ustekinumab (Stelara), golimumab (Simponi), ozanimod (Zeposia), and upadacitinib (Rinvoq) have not been evaluated in head-to-head trials to compare the efficacy and safety between these agents. Results from studies of each agent against placebo have shown statistically and clinically significant efficacy outcomes in inducing and maintaining remission during their respective pivotal trials. The net health benefit provided by adalimumab (Humira), tofacitinib (Xeljanz), ustekinumab (Stelara), and golimumab (Simponi) is incremental or better when evaluated against placebo. There is moderate certainty that ozanimod (Zeposia) provides promising but inconclusive net health benefit compared to placebo in patients with moderate to severe UC due to evidence being available from only one phase 3 trial and less established safety data compared to other UC treatment options.

III. The 2019 American College of Gastroenterology (ACG) clinical guideline on the management of ulcerative colitis in adults recommend oral systemic corticosteroids for induction of remission in moderate to severe disease (strong recommendation, moderate quality of evidence). TNF inhibitors (adalimumab, golimumab, and infliximab), vedolizumab (Entyvio), and tofacitinib (Xeljanz) are also recommended for induction of remission (strong recommendation, moderate quality of evidence). For maintenance of remission, thiopurines are recommended if remission was achieved after corticosteroid induction (conditional recommendation, low quality of evidence). The guidelines note a systematic review of 1,632 patients with ulcerative colitis demonstrated that azathioprine and mercaptopurine had a 76% mean efficacy in maintaining remission. If remission was achieved with anti-TNF therapy, vedolizumab (Entyvio), or tofacitinib (Xeljanz), clinical guidelines support continuing with the same agent to maintain remission (strong recommendation, moderate quality of evidence). The 2020 American Gastroenterology Association (AGA) guidelines make similar recommendations. Additionally, AGA recommends early use of biologic agents, rather than gradual step up after failure of 5-ASA in moderate to severe disease at high risk for colectomy. However, overall quality of evidence supporting this recommendation was rated as very low. Guidelines also note that for patients with less severe disease, 5-ASA therapy may still be a reasonable choice of therapy to start with. For maintenance of remission, AGA makes no recommendation in favor of, or against, using biologic monotherapy, rather than thiopurine monotherapy due to absence of evidence. As of May 2022, the guidelines have not been updated to include upadacitinib (Rinvoq).

IV. Patients who are primary non-responders to an anti-TNF therapy should be evaluated and considered for alternative mechanisms of disease control (e.g., in a different class of therapy) rather than cycling to another drug within the anti-TNF class. In patients with moderate to

severe active ulcerative colitis who had an initial response but subsequently lost efficacy to one anti-TNF therapy, clinical guidelines recommend alternative anti-TNF therapy (but not the biosimilar to the original brand) compared with no treatment for induction of remission.

V. The 2018 European Crohn's and Colitis Organization and European Society of Pediatric Gastroenterology, Hepatology, and Nutrition clinical guidelines recommend treatment with oral systemic corticosteroids if patients are in the higher end of the moderate disease range and treatment with thiopurines for maintaining remission in children who are corticosteroid-dependent or relapsing frequently despite 5-ASA treatment, and 5-ASA intolerant patients. The guidelines recommend infliximab (e.g., Remicade, Inflectra) in chronically active or steroid-dependent ulcerative colitis, uncontrolled by 5-ASA and thiopurines, for both induction and maintenance of remission. Adalimumab (Humira) or golimumab (Simponi) could be considered in those who initially respond but then lose response or intolerant to infliximab (e.g., Remicade, Inflectra), based on serum levels and antibodies. Vedolizumab (Entyvio) should be considered in chronically active or steroid-dependent patients as second-line biologic therapy after anti-TNF failure.

References

1. Tofacitinib (Xeljanz/Xeljanz XR) [Prescribing Information]. New York, NY; Pfizer Inc., Updated January 2022.
2. Upadacitinib (Rinvoq) [Prescribing Information]. North Chicago, IL; AbbVie. Updated May 2022.
3. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical Guideline: Ulcerative Colitis in Adults. *Am J Gastroenterol.* 2019;114(3):384-413.
4. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. Gastroenterology. 2020;158(5):1450-1461. doi:10.1053/j.gastro.2020.01.006
5. Paschos P, Katsoula A, Salanti G, et al. Systematic review with network meta-analysis: the impact of medical interventions for moderate-to-severe ulcerative colitis on health-related quality of life. Aliment Pharmacol Ther. 2018 Dec;48(11-12):1174-1185. doi: 10.1111/apt.15005. Epub 2018 Oct 30. PMID: 30378141.
6. Trigo-Vicente C, Gimeno-Ballester V, García-López S, et al. Systematic review and network meta-analysis of treatment for moderate-to-severe ulcerative colitis. Int J Clin Pharm. 2018 Dec;40(6):1411-1419. doi: 10.1007/s11096-018-0743-4. Epub 2018 Nov 26. PMID: 30478492.
7. Bonovas S, Lytras T, Nikolopoulos G, et al. Systematic review with network meta-analysis: comparative assessment of tofacitinib and biological therapies for moderate-to-severe ulcerative colitis. Aliment Pharmacol Ther. 2018 Feb;47(4):454-465. doi: 10.1111/apt.14449. Epub 2017 Dec 4. PMID: 29205421.
8. Turner et al. Management of Paediatric Ulcerative Colitis, Part 1: Ambulatory Care—An Evidence-based Guideline From European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition, Journal of Pediatric Gastroenterology and Nutrition: August 2018.

Atopic Dermatitis

Initial Evaluation

I. **Upadacitinib (Rinvoq)** may be considered medically necessary when the following criteria are met:
   A. Member is 12 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a dermatologist or an allergist; **AND**
   C. A diagnosis of **moderate to severe atopic dermatitis** when the following are met:
      1. Body surface area (BSA) involvement of at least 10%; **OR**
         i. Involves areas of the face, ears, hands, feet, or genitalia; **AND**
      2. Treatment with at least two of the following groups has been ineffective or not tolerated, or all are contraindicated:

i. Group 1: topical corticosteroids of at least medium/moderate potency (e.g., clobetasol, betamethasone, halobetasol)
ii. Group 2: topical calcineurin inhibitors (e.g., tacrolimus ointment, pimecrolimus cream)
iii. Group 3: topical PDE-4 inhibitor (crisaborole [Eucrisa]); **AND**

3. Documentation that a trial of systemic immunosuppressant, including a biologic, was ineffective, not tolerated, or all are contraindicated.

II. **Abrocitinib (Cibinqo)** may be considered medically necessary when the following criteria are met:
   A. Criteria I(A) - I(C) above are met; **AND**
   B. Treatment with dupilumab (Dupixent) and upadacitinib (Rinvoq) has been ineffective, contraindicated, or not tolerated.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat atopic dermatitis or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant); **AND**
IV. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in IGA score from baseline, BSA involvement, pruritis symptoms)

Supporting Evidence

I. Atopic dermatitis (AD), also known as atopic eczema, is an inflammatory skin condition most frequently occurring in pediatric patients. It manifests with pruritis, dry skin, crusting, and serous oozing causing chronic scratching which leads to blister formation, skin thickening (lichenification), fissuring, or lesions. This condition is associated with elevated serum IgE and it is often a comorbid condition with asthma and allergic conditions.
II. Treatments for mild-to-moderate AD include topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), phototherapy, and/or crisaborole (Eucrisa) – a PDE4 inhibitor. Symptomatic treatments include oral and topical antihistamines and sleep aids for nighttime pruritus. Treatment choice between these products is dependent on severity, location, and other patient specific factors (e.g., allergies, age). According to AAD guidelines, TCIs may be preferable to TCS in patients with recalcitrance to steroids, sensitive areas involved, steroid-induced atrophy, and long-term uninterrupted topical steroid use.
III. Treatment for moderate to severe disease not amenable to topicals includes systemic immunosuppressants (e.g., corticosteroids, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil), JAK inhibitors (e.g., abrocitinib, upadacitinib), and dupilumab (Dupixent), a biologic IgG4 that is FDA-approved for pediatrics and adults as a biologic option for moderate-to-severe AD. Currently, there are no head to head trials evaluating safety and/or

efficacy differences or superiority between biologic therapies in atopic dermatitis. Dupilumab (Dupixent) has an established safety and efficacy profile for the treatment of atopic dermatitis and is approved down to six years of age. Upadacitinib (Rinvoq) and abrocitinib (Cibinqo) have been evaluated and are FDA approved in patients down to 12 years of age.

IV. There may be patient specific scenarios in which the use of additional topical agents following failure of one class of topical agents would be impractical. Insight from dermatology specialists indicate that patients who have at least 15% BSA involvement, or involvement in sensitive areas (e.g., eyelids, axilla, genitals, gluteal cleft), and have severe disease are potential candidates for systemic biologic therapy. Severe disease, as defined by NICE guidelines, includes widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking, and alteration of pigmentation), and severe limitation of everyday activities and psychosocial functioning, nightly loss of sleep; severe disease can also be classified as physician's global assessment (PGA) score of 4.0. Additionally, administration of topical agents may become impractical for patients with high disease burden (BSA ≥ 20%), considering twice daily administration is necessary for non-steroid topical agents for optimal efficacy.

V. Upadacitinib (Rinvoq) is FDA approved in patients with moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable. Similarly, abrocitinib (Cibinqo) is FDA approved in adults and pediatric patients 12 years of age and older with refractory, moderate-to-severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable. Due to safety concerns, use of other systemic drugs is recommended prior to use of upadacitinib (Rinvoq) and abrocitinib (Cibinqo).

VI. There is lack of head-to-head clinical trial data for the AD FDA-approved therapies, and superior safety and efficacy of any product cannot be confidently concluded. Thus, it is reasonable, that pending no contraindication to therapy, preferred therapies be based on cost-effectiveness.

References

1. Silverberg JI, Simpson EL, Thyssen JP, Gooderham M. Efficacy and Safety of Abrocitinib in Patients With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol. 2020 Aug 1;156(8):863-873. doi: 10.1001/jamadermatol.2020.1406. PMID: 32492087; PMCID: PMC7271424.
2. Simpson EL, Sinclair R, Forman S. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet. 2020 Jul 25;396(10246):255-266. doi: 10.1016/S0140-6736(20)30732-7. PMID: 32711801.
3. American Academy of Dermatology – Guidelines of Care for the Management of Atopic Dermatitis (2014). Available at: https://www.aad.org/member/clinical-quality/guidelines/atopic-dermatitis
4. Eichenfield L., Tom, W., Chamlin S., et al. Guidelines of care for the management of atopic dermatitis. JAAD. 2014 Feb 1. 70(2): 338-351.
5. Clinical Review Report: Dupilumab (Dupixent): (Sanofi-Aventis Canada Inc.): Indication: Moderate-to-severe atopic dermatitis (AD) [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2018 Jul. Appendix 5, Validity of Outcomes Measures. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539234/
6. Dupixent [Prescribing Information]. Regeneron Sanofi Genzyme. Tarrytown, NF. October 2022.
7. Upadacitinib (Rinvoq) [Prescribing Information]. North Chicago, IL; AbbVie. Updated October 2022.
8. Eichenfield LF, Flohr C., et al. Efficacy and Safety of Abrocitinib in Combination With Topical Therapy in Adolescents With Moderate-to-Severe Atopic Dermatitis: The JADE TEEN Randomized Clinical Trial. JAMA Dermatol. 2021 Oct 1;157(10):1165-1173.
9. Abrocitinib (Cibinqo) [Prescribing Information]. New York, NY; Pfizer. Updated February 2023.

Crohn's Disease

Initial Evaluation

I. **Upadacitinib (Rinvoq)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a gastroenterologist; **AND**
   C. Diagnosis of **moderate to severe Crohn's disease; AND**
   D. Provider attestation or clinical documentation of at least one of the following:
      1. Treatment with systemic corticosteroids (e.g., prednisone, budesonide) has been ineffective, contraindicated, or not tolerated; **OR**
      2. Treatment with an immunomodulator (e.g., methotrexate, azathioprine, 6-mercaptopurine) has been ineffective, contraindicated, or not tolerated; **OR**
      3. Provider attestation or clinical documentation of high-risk disease (e.g., symptoms despite conventional therapy, obstruction, abscess, stricture, phlegmon, fistulas, resection, extensive bowel involvement, early age of onset, growth retardation); **AND**
   E. Treatment with one or more tumor necrosis factor (TNF) blockers [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], infliximab (Remicade) etc.] has been ineffective, not tolerated, or contraindicated

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat Crohn's disease or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, Infliximab, etc.)

Supporting Evidence

I. Upadacitinib (Rinvoq) is FDA approved for the treatment of moderate to severe Crohn's Disease (CD) based on safety and efficacy data from randomized-controlled trials. Certolizumab pegol (Cimzia), ustekinumab (Stelara), risankizumab (Skyrizi) and upadacitinib (Rinvoq) are FDA-approved in adults only, while adalimumab (Humira) is approved in patients six years of age and older.
II. Diagnosis of CD is based on a combination of clinical presentation, endoscopic, radiologic, histologic, and pathologic findings that demonstrate inflammation of the luminal GI tract. As such, it is recommended that diagnosis is made by a provider specialized in detecting and treating inflammatory bowel diseases, such as a gastroenterologist.

III. Therapeutic recommendations for patients with CD are established based upon disease location, disease severity, disease associated complications, and future disease prognosis. The goals of therapy are to induce remission, prevent relapse, and prevent occurrence of disease complications, such as stricture and fistula.

Moderate to severe CD

IV. According to the 2018 American College of Gastroenterology (ACG) guidelines patients with moderate to severe CD are considered to have failed to respond to treatment for mild to moderate disease, or those with more prominent symptoms of fever, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia. They have moderate to severely active endoscopic mucosal disease and disease activity corresponding to Crohn's Disease Activity Index (CDAI) score of 220-450.

V. Symptoms of CD do not correlate well with presence of active inflammation, and therefore should not be the sole guide for therapy. Objective evaluation by endoscopic imaging should be undertaken to avoid errors of under or overtreatment.

VI. Patients with CD are at risk of developing intestinal complications such as strictures, abscess, fistula, or phlegmon formation. According to the 2018 ACG guidelines features associated with high risk for progressive disease include age at diagnosis, initial extensive bowel involvement, ileal/ileocolonic or proximal gastrointestinal (GI) involvement, perianal/severe rectal disease, and patients presenting with a penetrating or stenosis disease phenotype.

VII. For patients with moderate to severe disease and those with moderate to high-risk disease, the 2018 ACG guidelines recommend treatment with oral corticosteroids used short term to induce remission (strong recommendation, moderate level of evidence). However, it is noted that one in five patients will become steroid refractory which is thought to be the result of unreliable efficacy in healing of the mucosa associated with steroids (weak recommendation, low level of evidence). Corticosteroids are also implicated in the development of perforating complications (abscess and fistula) and are relatively contraindicated in those patients. The 2021 American Gastroenterological Association (AGA) clinical guidelines make similar recommendations and suggest the use of corticosteroids in adult outpatients with moderate to severe CD over no treatment for induction of remission (conditional recommendation, moderate level of evidence).

VIII. In patients with moderate to severe CD who remain symptomatic despite current or prior corticosteroid therapy, 2018 ACG guidelines recommend immunomodulators such as azathioprine, 6-mercaptopurine (strong recommendation, moderate level of evidence), and methotrexate (conditional recommendation, low level of evidence) to be effective for maintenance of remission. Due to slow time to clinical response that may not be evident for as long as 12 weeks, these agents are not recommended for short-term induction. The 2021 AGA guidelines make similar suggestions and recommend use of thiopurines over no treatment for the maintenance of remission (conditional recommendation, low level of evidence).

IX. ACG guidelines recommend anti-TNF-alpha agents (infliximab [e.g., Remicade, Inflectra], adalimumab [Humira], certolizumab pegol [Cimzia]) in patients resistant to treatment with corticosteroids and refractory to thiopurines or methotrexate (strong recommendation, moderate level of evidence). Additionally, combination therapy of infliximab (e.g., Remicade, Inflectra) with immunomodulators (thiopurines) is more effective than treatment with either immunomodulators alone or infliximab (e.g., Remicade, Inflectra) alone in patients who are naïve to those agents (strong recommendation, high level of evidence). Recommendations are

also made regarding the use of vedolizumab (Entyvio), natalizumab (Tysabri), and ustekinumab (Stelara) without preference for one biologic over the other. The AGA guidelines recommend early introduction of biologics with or without immunomodulators rather than delaying their use until after failure of 5-aminosalicylates and/or corticosteroids; however, this recommendation is conditional with low certainty of evidence.

X. Adalimumab (Humira), ustekinumab (Stelara), certolizumab (Cimzia), infliximab (e.g., Remicade, Inflectra), vedolizumab (Entyvio), natalizumab (Tysabri), risankizumab (Skyrizi), and upadacitinib (Rinvoq) have not been studied in head-to-head trials to compare the efficacy and safety between these agents. Results from studies of each agent against placebo have shown statistically and clinically significant efficacy outcomes in inducing and maintaining remission during their respective pivotal trials. The net health benefit provided by all biologic agents FDA approved for the treatment of moderate to severe CD in adults is incremental or better when evaluated against placebo.

XI. The timing of introduction of biologic agents is a matter of debate and more studies are needed to assess stepwise approach versus earlier administration of biologic agents in patients with moderate to severe disease. The 2019 British Society of Gastroenterology guidelines suggest that systemic corticosteroids are still an effective initial therapy for uncomplicated luminal moderate to severe disease, regardless of disease location; however, every effort should be made to limit exposure (strong recommendation, high-quality evidence). In patients with an aggressive disease course, or high risk, poor prognostic factors, early introduction of biologics may be considered (weak recommendation, moderate-quality evidence). High risk features include extensive disease, complex (stricturing or penetrating disease), perianal fistulizing disease, age under 40 years at diagnosis, and the need for steroids to control index flare; however, the predictive power of these features is limited.

High-risk/severe CD

XII. Patients who are considered to have severe/fulminant disease are those with persistent symptoms despite introduction of conventional corticosteroids or biologic agents as outpatients, or individuals presenting with high fevers, persistent vomiting, evidence of intestinal obstruction, significant peritoneal signs such as involuntary guarding or rebound tenderness, cachexia, or evidence of an abscess. They have endoscopic or radiographic evidence of severe mucosal disease and disease activity corresponding to CDAI score of >450.

XIII. Collective evidence suggests that initial treatment with biologics may be considered for patients with the following disease features: severe CD (CDAI >450, evidence of intestinal obstruction, abscess, stricture, or phlegmon, and endoscopic or radiographic evidence of severe mucosal disease such as deep ulcerations), perianal fistulizing disease, and pre- and post-operative CD. Additional consideration may be given to patients presenting with other poor prognostic factors (e.g., extensive bowel involvement, early age of onset) and should be evaluated on case-by-case basis.

References

1. Adalimumab (Humira) [Prescribing Information] North Chicago, IL; AbbVie Inc., February 2021.
2. Certolizumab (Cimzia) [Prescribing Information] Smyrna, GA. UCB Inc., September 2019.
3. Ustekinumab (Stelara) [Prescribing Information] Raritan, NJ; Janssen Biotech, Inc. December 2020.
4. Risankizumab (Skyrizi) [Prescribing Information]. North Chicago, IL; AbbVie. Updated January 2021.
5. Upadacitinib (Rinvoq) [Prescribing Information]. North Chicago, IL; AbbVie. Updated October 2022.

6. Singh S, Fumery M, Sandborn WJ, et al. Systematic review and network meta-analysis: first- and second-line biologic therapies for moderate-severe Crohn's disease. Aliment Pharmacol Ther. 2018;48(4):394-409. doi:10.1111/apt.14852
7. Ma C, Lee JK, Mitra AR, et al. Systematic review with meta-analysis: efficacy and safety of oral Janus kinase inhibitors for inflammatory bowel disease. Aliment Pharmacol Ther. 2019;50(1):5-23. doi:10.1111/apt.15297
8. Nelson SM, Nguyen TM, McDonald JW, et al. Natalizumab for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2018;8(8):CD006097. Published 2018 Aug 1. doi:10.1002/14651858.CD006097.pub3
9. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. 2018;113(4):481-517.
10. Lamb, Christopher Andrew et al. "British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults." Gut vol. 68,Suppl 3 (2019): s1-s106. doi:10.1136/gutjnl-2019-318484
11. UpToDate, Inc. Overview of the management of Crohn disease in children and adolescents. UpToDate [database online]. Waltham, MA. Last updated September 14, 2021. Available at: http://www.uptodate.com/home/index.html.
12. van Rheenen PF, Aloi M, Assa A, et al. The Medical Management of Paediatric Crohn's Disease: an ECCO-ESPGHAN Guideline Update [published online ahead of print, 2020 Oct 7]. J Crohns Colitis. 2020;jjaa161. doi:10.1093/ecco-jcc/jjaa161
13. Feuerstein JD, Ho EY, Shmidt E, et al. AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease. Gastroenterology. 2021;160(7):2496-2508. doi:10.1053/j.gastro.2021.04.022

Investigational or Not Medically Necessary Uses

I. Combination use with topical and systemic JAK inhibitors
   A. The safety profile of systemic JAK inhibitors is continuing to develop; however, the FDA has issued cardiovascular and malignancy warnings. The true safety profile of ruxolitinib is unknown at this time, given the short trial duration and relatively small trial population. Utilizing a systemic JAK therapy in addition to topical JAK therapy (ruxolitinib) has unknown, and potentially additive, risks. Until further data are available to establish a safety profile with this combination, dual use will be disallowed.

II. COVID-19 or associated symptoms or complications
   A. The role of JAK-inhibitors in the treatment of COVID-19 is evolving and varies among available guidelines. Long-term data is not available and continuing therapy beyond hospitalization has not been evaluated for safety and efficacy.

III. Various dermatologic conditions (including, but not limited to plaque psoriasis, guttate psoriasis, vitiligo, dermatomyositis, lichen planus)
   A. Case reports suggest that the use of TNF inhibitors may induce flares when used for guttate psoriasis. Typical treatment involves phototherapy and topical corticosteroids/vitamin D analogs, with tonsillectomy or antibiotics used for more refractory disease. There is no established efficacy data for the use of biologics, JAK inhibitors, or targeted DMARDs in this setting at this time.
   B. A systematic review by Ciechanowich et al. evaluated the use of JAK inhibitors in psoriasis, atopic dermatitis, and vitiligo. Seventeen studies (11 randomized controlled trials, 4 case reports, 1 retrospective case series, and 1 open-label clinical trial) were included in the review and concluded that there is limited data to suggest the safety and efficacy of JAK inhibitors in various dermatologic diseases outside of FDA-approved indications. As of November 2022, deucravacitinib (Sotyktu) is the only JAK inhibitor FDA-approved to treat plaque psoriasis; upadacitinib (Rinvoq) and abrocitinib (Cibinqo) are FDA-approved to treat atopic dermatitis.

IV. Alopecia Areata/Alopecia Totalis/Alopecia Universalis
   A. Baricitinib (Olumiant) has FDA approval for alopecia areata; therapies for alopecia are in a category of medications that are not covered under the prescription benefit. Drugs used

for cosmetic purposes and/or to promote hair growth are excluded from coverage. Of note, not all JAK inhibitors have been evaluated or are FDA-approved for this condition.

V. Atopic Dermatitis – Olumiant (baricitinib)
   A. Two phase III, double-blind, multicenter monotherapy trials BREEZE-AD1 and BREEZE-AD2 studies concluded baricitinib 2mg, 4mg reached its primary endpoint of Validated Investigator's Global Assessment at week 16 compared to placebo. The manufacturer reports a statistical improvement in Investigator's Global Assessment (IGA) scores at week 16 compared to placebo, baricitinib improved clinical signs and symptoms in patients with moderate-to-severe AD within 16 weeks of treatment and induced rapid reduction of itch. The safety profile remained consistent with prior findings from baricitinib clinical development in AD, with no new safety concerns. The drug remains in clinical development and is considered experimental and investigational at this time. Three clinical trials are currently ongoing which may provide further confirmation of safety and efficacy.

VI. Familial Mediterranean Fever
   A. Current studies for Familial Mediterranean Fever, a subgroup of periodic fever syndrome, are limited to case reports. In evaluating current evidence available, quantitative evaluation of response to biologic treatments (e.g., tocilizumab, infliximab, etanercept, adalimumab, anakinra and canakinumab) is difficult to obtain, and therefore, difficult to assess true efficacy and safety. In the absence of controlled studies to evaluate the safety and efficacy of biologics in the treatment of patients with Familial Mediterranean Fever, the use of biologics in this setting would be considered experimental and investigational.

VII. Lupus Nephritis, Systemic Lupus Erythematosus (SLE), and Cutaneous Lupus Erythematosus (CLE)
   A. In a 24-week phase II RCT evaluated baricitinib in adults with highly active SLE exhibiting skin and joint symptoms despite the standard treatment, 314 patients were randomly assigned to receive placebo, baricitinib 2 mg, or baricitinib 4 mg. At week 24, baricitinib 4 mg dose (p=0.0414), but not the 2 mg dose, improved the signs and symptoms of active SLE. The short follow-up/study design limit the findings from this study.
   B. Lilly and Incyte have decided to end lupus development for Olumiant (baricitinib) after receiving topline efficacy data from two Phase III studies (SLE-BRAVE 1 and SLE-BRAVE 2) in adults with active lupus. While Olumiant (baricitinib) reached the primary endpoint in one trial (SLE-BRAVE 1), follow up trial (SLE-BRAVE 2) failed to meet the primary endpoint and neither trial achieved key secondary endpoints.

References

1. FDA Drug Safety and Availability. FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions. Published online September 27. https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death#:~:text=FDA%20is%20requiring%20new%20and,treat%20certain%20serious%20inflammatory%20conditions. Accessed November 22,2021.
2. National Institute of Allergy and Infectious Diseases (NIAID). Available from: https://clinicaltrials.gov/ct2/show/NCT04401579. Baricitinib plus remdesivir for hospitalized adults with covid-19. NLM Identifier: NCT04401579. Accessed November 22, 2021.

3. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalized adults with COVID-19 (Cov-barrier): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *The Lancet Respiratory Medicine*. Published online September 2021:S2213260021003313.
4. Cinats A, Heck E, Robertson L. Janus Kinase Inhibitors: A Review of Their Emerging Applications in Dermatology. Skin Therapy Lett. 2018;23(3):5-9.
5. Ciechanowicz P, Rakowska A, Sikora M, Rudnicka L. JAK-inhibitors in dermatology: current evidence and future applications. J Dermatolog Treat. 2019;30(7):648-658. doi:10.1080/09546634.2018.1546043
6. William Howe, MD. Treatment of atopic dermatitis (eczema). UpToDate [database online]. Waltham, MA. Last updated November 10, 2021.
7. Simpson EL, Lacour JP, Spelman L, et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. *Br J Dermatol*. 2020;183(2):242-255. doi:10.1111/bjd.18898
8. Guerra I, Algaba A, Pérez-calle JL, et al. Induction of psoriasis with anti-TNF agents in patients with inflammatory bowel disease: a report of 21 cases. *J Crohns Colitis*. 2012;6(5):518-523.
9. Bristol-Myers Squibb. Efficacy and safety study of abatacept to treat lupus nephritis. Available from: https://clinicaltrials.gov/ct2/show/results/NCT01714817?term=abatacept&cond=Lupus+Nephritis&rank=1. NLM Identifier: NCT01714817. Accessed June 21, 2019.
10. Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med*. 2005;352(4):351-361.
11. Booth A, Harper L, Hammad T, et al. Prospective study of TNFalpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. *J Am Soc Nephrol.* 2004;15(3):717-721.
12. Cetin P., Sari I., Sozeri B., et al. Efficacy of Interlukin-1 targeting Treatments in Patients with Familial Mediterranean Fever. Inflammation 2015, 368:1;27-31.
13. Ozen S., Demirkaya E., Erer B., et al. EULAR recommendation for the Management of Familial Mediterranean Fever. Annuals of Rheumatic Disease 2016:0; 1-8.
14. Nikiphorou E., Neocleous V., Phylactou L., et al. Successful use of tocilizumab in two cases of severe autoinflammatory disease with single copy of the Mediterranean Fever gene. Rheumatology 2017;56:9:1627-1628.
15. Fujikawa K., Migita K., Tsukada T., et al. Interleukin-6 targeting therapy in familial Mediterranean Fever. Clinical and experimental rheumatology 2013:31;150-151.
16. Akgul O., Kilic E., Kilic G., et al. Efficacy and safety of biologic treatments in Familial Mediterranean Fever. The American Journal of Medical Sciences 2013:346; 137-141.
17. Tumor Necrosis Factor Receptor-Associated Periodic Syndrome. National Organization for Rare Disorders. Updated 2019. Accessed January 25, 2021. https://rarediseases.org/rare-diseases/tumor-necrosis-factor-receptor-associated-periodic-syndrome/
18. Aksentijevich I, Master SL, Ferguson PJ, et al. An Autoinflammatory Disease with Deficiency of the Interleukin-1–Receptor Antagonist. N Engl J Med. 2009;360(23):2427-2437.
19. Jesus AA, Goldbach-Mansky R. IL-1 Blockade in Autoinflammatory Syndromes. Annu. Rev. Med. 2014. 65:223–244.
20. Wallace DJ, Furie RA, Tanaka Y, et al. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial [published correction appears in Lancet. 2018 Aug 11;392(10146):476]. *Lancet*. 2018;392(10143):222-231. doi:10.1016/S0140-6736(18)31363-1
21. AbbVie. Available from: https://clinicaltrials.gov/ct2/show/NCT03978520. A Study to Investigate the Safety and Efficacy of Elsubrutinib and Upadacitinib Given Alone or in Combination in Participants With Moderately to Severely Active Systemic Lupus Erythematosus (SLE) (SLEek). NLM Identifier: NCT03978520. Accessed November 22, 2021.
22. Eli Lilly and Company [online press release]. Updates on OLUMIANT® (baricitinib) Phase 3 lupus program and FDA review for atopic dermatitis. Available at: https://investor.lilly.com/news-releases/news-release-details/updates-olumiantr-baricitinib-phase-3-lupus-program-and-fda. Updated January 28, 2022.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy	Disease state
Chronic Inflammatory Disease Policy	Rheumatoid Arthritis
	Polyarticular Juvenile Idiopathic Arthritis (PJIA)
	Enthesitis-Related Arthritis (ERA)
	Systemic Juvenile Idiopathic Arthritis (SJIA)

	Psoriatic Arthritis
	Ankylosing Spondylitis
	Non-radiographic Axial Spondyloarthritis
	Plaque Psoriasis
	Crohn's Disease
	Ulcerative Colitis
	Behcet's Disease (i.e., Behcet Syndrome)
	Hidradenitis Suppurativa
	Uveitis and Panuveitis
	Giant Cell Arteritis
	Cryopyrin-Associated Periodic Syndromes (CAPS)
	Recurrent Pericarditis
	Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)
ruxolitinib (Jakafi, Opzelura) Policy	Intermediate or high-risk myelofibrosis
	Polycythemia vera
	Graft-Versus-Host Disease
	Atopic dermatitis
fedratinib (Inrebic) Policy	Myelofibrosis
Dupilumab (Dupixent) Policy	Atopic dermatitis
Tralokinumab (Adbry) Policy	Atopic dermatitis
Tapinarof (Vtama)	Plaque psoriasis

Policy Implementation/Update

Action and Summary of Changes	Date
Live 04/01/2024: addition of select biosimilars (Hadlima and adalimumab-adaz) as preferred products, removal of brand Humira as a preferred product. Change to ulcerative colitis criteria to require trial of at least one corticosteroid or immunomodulator; change to Crohn's disease criteria to require trial of at least one corticosteroid or immunomodulator and change to define high-risk Crohn's disease and remove severe Chron's disease	02/2024
Live 01/2024: Added guselkumab (Tremfya) as a preferred product.	11/2023
Updated Cibinqo age requirements. Update to supporting evidence.	04/2023
Live 06/2023: Added criteria to include new indication for Rinvoq in the setting of Crohn's disease. Updated quantity limit table to include new indication of Crohn's disease for Rinvoq. Updated initial authorization for Rinvoq XR 45mg tablets to two months for Ulcerative Colitis and three months for Crohn's disease, added fill limit of three fills per year for CD. Updated supporting evidence section and references for Crohn's disease.	03/2023
Review conducted. Update to supporting evidence.	02/2023
Effective 01/01/2023 - Cibinqo in setting of atopic dermatitis: updated to require trial of Dupixent AND Rinvoq, previously only listed Rinvoq	12/2022
Added criteria to include new indication for Rinvoq in the setting at non-radiographic spondyloarthritis. Updated supporting evidence and references for AS and nr-axSpA sections. Updated wording of renewal criteria regarding combination biologic use to reflect specific disease state referenced. Updated E/I supporting evidence for use of JAK inhibitors in dermatologic conditions. Updated related policies section.	11/2022
Addition of new molecular entity, Sotyktu in plaque psoriasis	08/2022
Added new indication for Rinvoq in the setting of active ankylosing spondylitis, updated supportive evidence, and reference section. Added new indication of alopecia areata for baricitinib (Olumiant®) noting this is an excluded indication.	06/2022
Added Rinvoq's new indication of Ulcerative Colitis, updated supporting evidence section; added new criteria for Rinvoq in the setting of Atopic Dermatitis to require use of systemic immunosuppressants, including biologic agents first to align per label; added Olumiant's indication of COVID-19 and new tablet strength in the QL table; removed AS from E/I section given recent FDA-approval of Rinvoq in AS; updated formatting.	05/2022

Added Cibinqo for the setting of Atopic Dermatitis, built out the Atopic Dermatitis criteria section in the policy for Cibinqo and Rinvoq with new FDA approvals. Updated PJIA supporting evidence and references to further clarify guidelines and treatment algorithm and align with Chronic Inflammatory Disease policy.	03/2022
Added new indications for Rinvoq in setting of PsA and Xeljanz in AS. Updated AS supporting evidence and references to include 2019 guideline update. Added criteria for all diagnoses requiring trial of TNF blockers prior to JAK inhibitor therapy as recommended by FDA labeling. Experimental and investigational section updated to include warning on combination of topical and oral JAK inhibitors and alopecia areata. Added new Rinvoq 30mg tablet availability for atopic dermatitis.	02/2022
Created the Janus Associated Kinase Inhibitor policy. Added Rinvoq and Xeljanz to preferred product mix (effective 1/1/2022). Added Related Policies section.	12/2021
Previous policy changes (relevant from Chronic Inflammatory Policy)	
Updated criteria for ulcerative to modify the weight requirement for Humira to a specific age group. Added a requirement to try and fail TNF blockers before allowing treatment with tofacitinib (Xeljanz) as recommended by FDA labeling. Supporting evidence and references updated.	06/2021
Updated PA policy to include FDA approvals for Xeljanz for PJIA. Updated supporting evidence section with clinical trial data	11/2020
Updated the products for psoriatic arthritis to include guselkumab (Tremfya). Updated the supporting evidence section for psoriatic arthritis to reflect no changes in the guidelines with regard to guselkumab (Tremfya).	08/2020
Criteria updated to new policy format. Specific changes include: <u>Rheumatoid Arthritis</u> • Removed the number of joints and duration of disease question as evidence and guidelines did not support the requirement • Removed requirements for diagnosis due to varying methods to diagnose and limited value of this question from health plan standpoint • Clarified use of oral DMARD requirement may be bypassed if all of them are contraindicated • Added newly approved upadacitinib (Rinvoq) as a non-preferred alternative <u>Polyarticular Juvenile Idiopathic Arthritis (PJIA)</u> • Removed the number of joints and duration of disease question as evidence and guidelines did not support the requirement • Added route to approval of Actemra as Actemra was previously in a separate policy <u>Psoriatic Arthritis</u> • Added requirement of the presence of active severe disease and provided specific indicators of severe disease • Added clinical note: "If a patient has a diagnosis of both plaque psoriasis and psoriatic arthritis, approval of the requested medication can be made as long as the patient fulfills the criteria for at least one of the disease states and associated medication criteria." <u>Ulcerative Colitis</u> • Added age of 18 years or older • Addition of trial of thiopurine for at least 8 weeks	08/2019
Criteria update: Increased initial approval from 3 months to 6 months, updated initial QL to reflect 6 month approval duration. Added new Xeljanz IR 10mg tablet availability. Added baricitinib (Olumiant) as an option for the treatment of rheumatoid arthritis after trial and failure of a TNF antagonist.	07/2018
Criteria update: Added new Kevzara auto injector formulation, Xeljanz new indication in ulcerative colitis, added Cimzia new indication in plaque psoriasis, minor formatting edits.	06/2018
New Criteria Set – consolidated from all biologic agents along with Otezla and Xeljanz criteria sets. Within this new criteria set, here are the following updates: 1. 18 years of age requirement has been removed for Stelara as it has now been FDA approved for pediatric plaque psoriasis. 2. New FDA approved indication of psoriatic arthritis has been added for Xeljanz/Xeljanz XR and Taltz	01/2018

3. The question regarding dual therapy has been refined to encompass the language of biologics and other non-biologics (e.g. Otezla and Xeljanz). 4. The question regarding DMARDs has been refined to only include agents that are administered non-biologic, non-specialty and that are administered orally. 5. For the indication of plaque psoriasis, the question addressing the trial of UVB has been combined with the trial of DMARDs.	

Policy Type: PA/SP Pharmacy Coverage Policy: UMP034

Description
Tafamidis meglumine (Vyndaqel) and tafamidis (Vyndamax) are orally administered transthyretin stabilizers.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
tafamidis meglumine (Vyndaqel)	20 mg capsules	Cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis	120 capsules/30 days	206608
tafamidis (Vyndamax)	61 mg capsules		30 capsules/30 days	206614

Initial Evaluation

I. Tafamidis meglumine (Vyndaqel) and tafamidis (Vyndamax) may be considered medically necessary when the following criteria below are met:
   A. Member 18 years or older; **AND**
   B. Medication is prescribed by or in consultation with a neurologist or cardiologist; **AND**
   C. Tafamidis meglumine (Vyndaqel) or tafamidis (Vyndamax) will not be used in combination with other agents for the treatment of transthyretin-mediated amyloidosis [i.e. inotersen (Tegsedi), patisiran (Onpattro)]; **AND**
   D. A diagnosis of **cardiomyopathy of wild type (ATTRwt-CM) or hereditary transthyretin-mediated amyloidosis (hATTR-CM)** when the following are met:
      1. Confirmed transthyretin-mediated amyloidosis by one of the following:
         i. Documented presence of amyloid deposit by biopsy; **OR**
         ii. Presence of transthyretin precursor protein confirmed by scintigraphy (i.e. radiotracer 99m technetium pyrophosphate (99mTc-PYP))

      AND
      2. History of heart failure; **AND**
      3. Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness > 12 mm; **AND**
      4. New York Heart Association (NYHA) functional class I-III; **AND**
      5. No prior history of liver or heart transplantation

II. Tafamidis meglumine (Vyndaqel) and tafamidis (Vyndamax) is considered <u>not medically necessary</u> when used for all other conditions, including but <u>not limited to</u>:

A. Cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in members with NYHA functional class IV

III. Tafamidis meglumine (Vyndaqel) and tafamidis (Vyndamax) is considered investigational when used for all other conditions, including but not limited to:
   A. Polyneuropathy of hereditary transthyretin-mediated amyloidosis (ATTR-PN) or familial amyloid polyneuropathy (FAP)
   B. Primary (light chain) amyloidosis

Renewal Evaluation

I. Member has previously received treatment with tafamidis meglumine (Vyndaqel) or tafamidis (Vyndamax); **AND**
II. Documentation that the patient has experienced a positive clinical response therapy (e.g., reduced cardiovascular hospitalizations, improved quality of life, slowing of disease progression, etc.); **AND**
III. No prior history of liver or heart transplantation; **AND**
IV. New York Heart Association (NYHA) functional class I-III; **AND**
V. Tafamidis meglumine (Vyndaqel) or tafamidis (Vyndamax) will not be used in combination with other agents for the treatment of transthyretin-mediated amyloidosis [i.e. inotersen (Tegsedi), patisiran (Onpattro)].

Supporting Evidence

I. Tafamidis meglumine (Vyndaqel) and tafamidis (Vyndamax) are transthyretin stabilizers FDA approved for the treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization.
II. Vyndamax (tafamidis) was developed for patient convenience. Vyndaqel (tafamidis meglumine) and Vyndamax (tafamidis) are not substitutable on a per-mg basis.
III. Tafamidis meglumine (Vyndaqel) was studied in a phase 3, multicenter, international, randomized, double-blind, placebo-controlled study in 441 patients with wild type or hereditary ATTR-CM (ATTR-ACT trial). The trial met its primary endpoint, demonstrating a significant reduction ($p=0.0006$) in all-cause mortality and frequency of cardiovascular-related hospitalizations ($p<0.0001$) in the pre-specified pooled tafamidis meglumine (Vyndaqel) 20-mg and 80-mg groups versus placebo at 30 months. Tafamidis meglumine (Vyndaqel) also showed a lower rate of decline in distance for the 6-minute walk test and lower rate of decline in the Kansas City Cardiomyopathy Questionnaire Overall Summary score (KCCQ-OS). Of note, subgroup analysis of patients identified as NYHA class III at baseline did not show a reduction in all-cause mortality or cardiovascular related hospitalizations. In the NYHA class III patients, cardiovascular related hospitalizations were actually higher among patients receiving tafamidis meglumine (Vyndaqel) than those receiving placebo.
IV. NYHA Classification - The Stages of Heart Failure:

- Class I - No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
- Class II - Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
- Class III - Marked limitation in activity due to symptoms. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain. Comfortable at rest.
- Class IV - Severe limitations. Inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

V. Patients included in the pivotal trial had a history of heart failure, evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness > 12 mm, and confirmed transthyretin-mediated amyloidosis by documented presence of amyloid deposit by biopsy and/or presence of transthyretin precursor protein confirmed by scintigraphy.

VI. Nuclear scintigraphy is a newer, less invasive diagnostic method thought to improve the diagnosis rate of ATTR-CM. Though use of this diagnostic tool may be limited, due to the specialized nature of the protocol and the skill needed for interpretation of the results. There are two radiolabeled phosphonates that have been studied most in this setting, ^{99m}Tc-pyrophosphate (^{99m}Tc-PYP) in the US and ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) in Europe. In the US, the radiotracer 99m technetium pyrophosphate, or ^{99m}Tc-PYP, is not FDA-approved for the diagnosis of ATTR-CM, but it is increasingly used by the medical community.

VII. Patients were excluded if they had NYHA Class IV heart failure, primary amyloidosis, or a history of liver or heart transplantation.
- Primary amyloidosis was excluded as this diagnosis is considered emergent and entails a different treatment approach consisting of chemotherapy.
- Before the availability of tafamidis the management of ATTR-CM consisted of symptomatic treatment of heart failure symptoms and liver and/or heart transplantation. Orthotopic liver transplant (OLT) is one of the most established, potentially curative treatment options for some patients with ATTR-CM, specifically patients with early-stage hATTR. Orthotopic heart transplant (OHT), alone or in combination with OLT, may be a therapeutic option for select patients with ATTR-CM.
- Tafamidis meglumine (Vyndaqel) is designed to target the underlying disease process in ATTR-CM through inhibition of the TTR tetramer dissociation. This forms the rationale for the use of tafamidis meglumine to slow disease progression. The progressive nature of the disease underscores the importance of early diagnosis and suggests tafamidis meglumine treatment may be most beneficial when initiated in early stages of the disease when heart failure is less severe and may be more easily reversed compared with later stages. Disease-modifying treatments, such as tafamidis meglumine (Vyndaqel) may be less effective once amyloid deposition has caused irreversible organ damage.

VIII. Tafamidis meglumine (Vyndaqel) was studied as monotherapy. There is no data on the use of combination therapy with other medications indicated for different types of amyloid disease.

IX. Within the pivotal trial results, a greater proportion of patients in the tafamidis meglumine group either improved upon or remained at their respective NYHA baseline classification compared with patients in the placebo group.

Investigational or Not Medically Necessary Uses

I. Cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in members with NYHA functional class IV
   A. In the ATTR-ACT trial, patients with NYHA Class IV were excluded from the pivotal trial. The progressive nature of the disease underscores the importance of early diagnosis and suggests tafamidis meglumine treatment may be most beneficial when initiated in early stages of the disease when heart failure is less severe and may be more easily reversed compared with later stages. Disease-modifying treatments, such as tafamidis meglumine (Vyndaqel) may be less effective once amyloid deposition has caused irreversible organ damage.

II. Polyneuropathy of hereditary transthyretin-mediated amyloidosis or familial amyloid polyneuropathy (FAP)
   A. Coelho et al. 2012 reported no significant changes in patients with early-stage V30M transthyretin familial amyloid polyneuropathy (TTR-FAP) as coprimary endpoints were not met in the ITT population.
   B. The US FDA did not approve tafamidis meglumine (Vyndaqel) use in FAP during a filing in 2012, due to limited efficacy data. The agency requested the completion of a second efficacy study to establish substantial evidence of effectiveness prior to an approval.

III. Primary (light chain) amyloidosis
   A. In the pivotal trial (ATTR-ACT), patients with primary amyloidosis were excluded. Primary amyloidosis is caused by a bone marrow disorder. Treatment consists of chemotherapy or bone marrow transplant.

References

1. Vyndamax (tafamidis) [prescribing information]. New York, NY: Pfizer Labs; May 2019.
2. Vyndaqel (tafamidis meglumine) [prescribing information]. New York, NY: Pfizer Labs; May 2019.
3. Buxbaum J. Oligonucleotide Drugs for Transthyretin Amyloidosis. NEJM. 2018;379(1):82-85. doi:10.1056/NEJMe1805499.
4. Center for Drug Evaluation and Research. Tegsedi (inotersen) Summary Review. Application Number: 211172Orig1s000. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211172Orig1s000SumR.pdf
5. Coelho T, Ericzon B, Falk R, et al. A Guide to Transthyretin Amyloidosis. Available at: https://amyloidosis.org/sites/default/files/pdf-docs/pages/resources/2023-03/2018%20ATTR.pdf.
6. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013;8(1):1-18. doi:10.1186/1750-1172-8-31.
7. 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.
8. U.S. FDA Approves VYNDAQEL and VYNDAMAX for Use in Patients with Transthyretin Amyloid Cardiomyopathy, a Rare and Fatal Disease. [press release]. Pfizer Inc. May 6, 2019.
9. Coelho T, Maia LF, Martins da silva A, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. Neurology. 2012;79(8):785-92.

10. Barroso FA, Judge DP, Ebede B, et al. Long-term safety and efficacy of tafamidis for the treatment of hereditary transthyretin amyloid polyneuropathy: results up to 6 years. Amyloid. 2017;24(3):194-204.
11. FDA Issues Complete Response Letter For Pfizer's Tafamidis Meglumine New Drug Application [press release]. Pfizer Inc, June 18, 2012
12. The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels, 9th ed, Little, Brown & Co, Boston, 1994. p.253.
13. AL Amyloidosis. Amyloidosis Foundation website. Available at: www.amyloidosis.org/facts/al/#faqs
14. Vyndaqel (tafamidis meglumine) AMCP Dossier. New York, NY: Pfizer Labs May 24, 2019

Policy Implementation/Update:

Date Created	May 2019
Date Effective	August 2019
Last Updated	
Last Reviewed	

Action and Summary of Changes	Date

Policy Type: PA Pharmacy Coverage Policy: UMP065

Split Fill Management*

Description

Talazoparib (Talzenna) is an orally administered poly (ADP-ribose) polymerase (PARP) inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: Twelve months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
talazoparib (Talzenna)	Breast cancer, locally advanced or metastatic, BRCA-mutated Prostate cancer, metastatic castration-resistant, homologous recombination repair (HRR) gene-mutated	0.1 mg capsules	30 capsules/ 30 days*
		0.25 mg capsules	
		0.3 mg capsules	
		0.5 mg capsules	
		0.75 mg capsules	
		1 mg capsules	

** Quantity limit exceptions are limited to dose reductions and clinician review*

Initial Evaluation

I. **Talazoparib (Talzenna)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a specialist in oncology; **AND**
   C. Member has not had disease progression on prior PARP inhibitor therapy (e.g., niraparib [Zejula], rucaparib [Rubraca], olaparib [Lynparza]); **AND**
   D. A diagnosis of **locally advanced (stage III) or metastatic (stage IV) breast cancer** when the following are met:
      1. Medication will be used as monotherapy; **AND**
      2. Documented deleterious (pathogenic) or suspected deleterious (likely pathogenic) germline BRCA mutation as determined by FDA approved diagnostic testing; **AND**
      3. Prior treatment with an anthracycline (e.g., doxorubicin) and/or a taxane (e.g., paclitaxel) was ineffective, unless contraindicated; **AND**
      4. For hormone receptor-positive (ER/PR+) disease, member has had disease progression on endocrine therapy; **OR**
         i. Endocrine therapy has been deemed inappropriate by the treating healthcare provider
   E. A diagnosis of **metastatic, castration-resistant prostate cancer (mCRPC)**; **AND**

1. Evidence of disease progression despite therapy with a gonadotropin-releasing hormone analog (GnRH) or bilateral orchiectomy; **AND**
2. The member has not had disease progression on a second-generation antiandrogen agent (e.g. abiraterone, enzalutamide (Xtandi), apalutamide (Erleada), darolutamide (Nubeqa)); **AND**
3. Talazoparib (Talzenna) will be used in combination with enzalutamide (Xtandi); **AND**
4. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) alteration in the BRCA1 or BRCA2 gene; **AND**
    i. Documentation of intolerance or contraindication to generic abiraterone in combination with olaparib (Lynparza) (use of generic abiraterone 250 mg tablets required); **OR**
5. The member has an alteration in an HRR gene that is not BRCA1 or BRCA2 (e.g., *ATM, ATR, CDK12*, etc.)

II. Talazoparib (Talzenna) is considered investigational when used for all other conditions, including but not limited to:
    A. When used in combination with any other chemotherapy or targeted therapy
    B. Early-stage breast cancer
    C. Ovarian cancer, fallopian tube, and peritoneal cancer
    D. Lung cancer
    E. Prostate cancer, non-metastatic, castration-sensitive, and without HRR mutation

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Clinical documentation of response to treatment (e.g., stabilization of disease, decrease in tumor size or tumor spread, lack of disease progression); **AND**
    A. **Locally advanced (stage III) or metastatic (stage IV) breast cancer;**
        1. Talazoparib (Talzenna) will not be used in combination with other anti-cancer agents (outside of gonadotropin releasing hormone agonist [e.g., leuprolide], endocrine therapy [e.g., anastrozole, tamoxifen, fulvestrant]; **OR**
    B. **Metastatic, castration-resistant prostate cancer (mCRPC);**
        1. Talazoparib (Talzenna) will be used in combination with enzalutamide (Xtandi)

Supporting Evidence

Breast Cancer

I. Talazoparib (Talzenna) is FDA-approved for the treatment of adults with germline BRCA mutated (gBRCAm), HER2-negative, locally advanced or metastatic disease.
II. The efficacy and safety of talazoparib (Talzenna) monotherapy was demonstrated in an open-label randomized, trial (EMBRACA) which enrolled adult patients that had a deleterious or suspected deleterious germline BRCA1/2 mutation detected by testing with BRACAnalysis.

III. Overall, 431 patients were randomized 2:1 to receive talazoparib or chemotherapy of the provider's choice (capecitabine, eribulin, gemcitabine or vinorelbine); 287 patients received talazoparib and 144, chemotherapy. Baseline characteristics of both groups were generally similar, but the talazoparib included a higher number of patients with a baseline Eastern Cooperative Oncology Group (ECOG) performance score of 1 or 2 and a higher number of patients whose disease progressed to advanced within 12 months of initial diagnosis.

IV. To be included in the EMBRACA study, patients had received no more than three previous cytotoxic regimens for advanced breast cancer, and they had received previous treatment with a taxane or an anthracycline, or both, unless contraindicated. Additionally, previous neoadjuvant or adjuvant platinum-based therapy was allowed, provided the patient had a disease-free interval for at least six months after the last dose. Patients were excluded if they had disease progression while receiving platinum chemotherapy for advanced breast cancer (i.e., progression of disease within approximately eight weeks after the last dose). Third, patients included in the study had no more than three prior therapies in the advanced breast cancer setting. More than two therapies in other settings (e.g. neoadjuvant, adjuvant) do not apply. However, as current guidelines move to testing for targeted therapies once diagnosed, the likelihood of patients using over one line of therapy is rare.

V. The primary endpoint of the study was radiologic progression-free survival (PFS) done via imaging at baseline, every 6 weeks until week 30, and then every 9 weeks after. The median progression-free survival was significantly longer among patients in the talazoparib group than among patients in the standard-therapy group (8.6 months [95% confidence interval {CI}, 7.2 to 9.3] vs. 5.6 months [95% CI, 4.2 to 6.7]; hazard ratio for disease progression or death, 0.54; 95% CI, 0.41 to 0.71; P<0.001).

VI. Although prior endocrine-based therapy was not required in the EMBRACA trial, 90.4% of patients had progressed on endocrine-based therapy before being treated with talazoparib (Talzenna), and 100% had received prior chemotherapy for HR+ disease. The standard treatment approach for HR+ disease is to first target the hormone pathway (unless considered inappropriate), then consider single agent chemotherapy or PARP inhibitor if there is a progression on endocrine-based therapy.

VII. The National Comprehensive Cancer Network (NCCN) breast cancer guideline lists the PARP inhibitors [talazoparib (Talzenna) and olaparib (Lynparza)] as Category 1 options for previously treated recurrent or metastatic germline BRCA mutated breast cancer. EMBRACA clinical program included 56% patients with ER/PR+, HER2- advanced or metastatic breast cancer, while 44% had triple-negative breast cancer (TNBC). Thus, talazoparib (Talzenna) may be considered a practical treatment option for patients with TNBC. However, presence of germline BRCA1 or BRCA2 mutation is a pre-requisite for initiating treatment with talazoparib (Talzenna).

VIII. In the EMBRACA trial, adverse reactions were reported at a higher incidence in those receiving talazoparib than placebo-chemotherapy arm. Sixty-five percent of patients taking talazoparib versus 50% chemotherapy experienced ADE and dose reductions due to any cause occurred in 53% of talazoparib patients versus chemotherapy patients. Due to the high incidence of this, split fill is applied to the medication upon initial approval.

IX. Dose adjustments are common with talazoparib (Talzenna) and the as the product it is flat priced (i.e., there is a single fixed price for *each* tablet regardless of dosage strength). When

possible, patients should be dose optimized to once a day dosing of an appropriate strength versus allowing multiple tablets of a lower dose.

Prostate Cancer

I. Talazoparib (Talzenna) is FDA approved for the treatment of metastatic castration resistant prostate cancer (mCRPC) with HRR-gene mutation.

II. The safety and efficacy of talazoparib (Talzenna) is demonstrated in the TALAPRO-2 trial, which is a randomized, double blind, placebo-controlled, phase 3 trial. Eight hundred and five patients were randomized 1:1 to either receive enzalutamide in combination with talazoparib (Talzenna) or placebo. They were further stratified by previous novel hormonal therapy/docetaxel and HRR gene-alteration status. The primary outcome was radiographic progression free survival (rPFS) assessed by blinded independent central review per RECIST 1.1 (soft tissue disease) and Prostate Cancer Clinical Trials Working Group 3 (bone disease). Treatment with talazoparib/enzalutamide resulted in a 37% lower risk of radiographic progression or death compared to placebo/enzalutamide (HR 0.63; 95% CI 0.51–0.78; p<0.0001). The most common adverse effects in the treatment group were anemia (66%), neutropenia (36%), and fatigue (34%).

III. One of the key inclusion criteria in TALAPRO-2 was bilateral orchiectomy or ongoing ADT with a GnRH agonist/antagonist. ADT was required to be continued throughout the study for patients who had not undergone bilateral orchiectomy. The safety and efficacy of Talzenna/enzalutamide in patients with prior treatment and progression on a second-generation AR inhibitor (i.e., enzalutamide, apalutamide and darolutamide) has not been established as these patients were excluded from the trial.

IV. The PROpel trial investigating Lynparza versus placebo in combination with abiraterone targeted a similar patient population as TALAPRO-2, men with metastatic castration resistant prostate cancer with HRR related mutations. The treatment group demonstrated a reduced risk of disease progression or death by 34% versus abiraterone alone (HR 0.66; 95% CI 0.54-0.81; p<0.0001). As of August 2023, head-to-head trials have not been conducted to suggest superiority of one regimen over the other. Abiraterone is currently available as a generic formulation. Lynparza/abiraterone was FDA approved for this indication in patients harboring a *BRCAm*, while Talzenna/enzalutamide carries a broader FDA approval encompassing all *HRRm* (e.g., ATM, ATR, CDK12, etc.)

V. DNA repair anomalies known as homologous recombination repair gene mutations (HRRm) are identified in approximately 25% of patients with mCRPC. HRR gene mutations can consist of mutations in *ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, or RAD51C*. Approximately 10-15% of patients with mCRPC have the BRCA1/BRCA2 gene mutations. These mutations have been associated with more aggressive disease and poor patient outcomes.

Investigational or Not Medically Necessary Uses

I. The efficacy and safety of talazoparib (Talzenna) in combination with other chemotherapy or immunotherapy agents have not been evaluated. Talazoparib (Talzenna) is indicated as monotherapy.

II. There is no evidence to support the use of a subsequent PARP inhibitor following the progression of disease on another PARP inhibitor.

III. Due to its mechanism of action, there is interest in using talazoparib (Talzenna) in other cancers such as ovarian cancer, and lung cancer; however, studies are still ongoing and use outside of BRCA mutated advanced or metastatic breast cancer is considered investigational.
IV. Additionally, there is a lack of evidence supporting the use of talazoparib (Talzenna) in early breast cancer (e.g., neoadjuvant or adjuvant treatment).

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Talzenna [Prescribing Information]. New York, NY: Pfizer. October 2018. Revised 9/2021
2. Litton J, Rugo H, Ettl J, et al. Talazoparib in patients with advanced breast cancer and germline BRCA mutation. N Engl J Med 2018;379:753-63
3. NCCN Clinical Practice Guideline in Oncology: Breast Cancer. Version 2.2022-December 20,2021 National Comprehensive Cancer Network. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Updated 12/2021. Accessed April 18, 2022.
4. UpToDate, Inc. Systemic treatment of metastatic breast cancer in women: Chemotherapy. UpToDate [database online]. Waltham, MA. Available at: http://www.uptodate.com/home/index.html. Updated August 21, 2017. Accessed December 27, 2018.
5. National Institutes of Health, Clinicaltrials.gov [website]. [cited periodically]; Available from: www.clinicaltrials.gov
6. Agarwal N, Azad AA, Carles J, et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial [published online ahead of print, 2023 Jun 2]. Lancet. 2023;S0140-6736(23)01055-3. doi:10.1016/S0140-6736(23)01055-3
7. National Comprehensive Cancer Network. Prostate Cancer (Version 2.2023) NCCN. July 17, 2023. Accessed July 20, 2023. prostate.pdf (nccn.org)

Related Policies

Policy Name	Disease state
Cyclin-Dependent Kinase (CDK) 46 Inhibitors	Breast cancer, HER2-negative, HR-positive, advanced or metastatic, early-stage breast cancer
alpelisib (Piqray)	PIK3CA mutation, HR+, HER2-, advanced or metastatic breast cancer
lapatinib (Tykerb)	Breast cancer, HER2 over expression, advanced or metastatic in combination with capecitabine after prior therapy OR postmenopausal women, in combination with letrozole
neratinib (Nerlynx)	Breast cancer, early stage, HER2-positive, following trastuzumab OR advanced, metastatic
olaparib (Lynparza)	Breast cancer, metastatic, HER2-negative, germline BRCA-mutated (gBRCAm) Prostate cancer, metastatic castration-resistant (mCRPC)
tucatinib (Tukysa)	Metastatic breast cancer
Second Generation Anti-Androgen Agents	Prostate cancer

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated step through Lynparza/abiraterone for mCRPC to delineate between patients with BRCAm vs HRRm; updated supporting evidence	02/2024
Added expanded indication for the treatment of mCRPC in combination with enzalutamide; updated supporting evidence	09/2023
Streamlined clinical criteria to better reflect our current PARP policies. Removed requirement of HER2 negative disease. Removed confirmation member is not platinum refractory. Removed requirement of maximum number of prior cytotoxic regimens. Improved supporting evidence section for better clinical support. Added related policies.	08/2022
Previous Reviews	02/2019

Policy Type: PA Pharmacy Coverage Policy: UMP262

Description

Tapinarof (Vtama) cream is a topical aryl hydrocarbon receptor agonist.

Length of Authorization

- Initial: Six months
- Renewal: 12 months
    i. One three-month quantity exception approval allowed per lifetime, when applicable criteria are met.

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
tapinarof (Vtama)	Plaque Psoriasis	1% topical cream	60 grams/30 days*

**Quantity exceptions not allowed on initial approval*

Initial Evaluation

I. **Tapinarof (Vtama) cream** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Diagnosis of plaque psoriasis; **AND**
   C. Treatment with at least one agent from three different topical medication classes below has been ineffective or not tolerated, unless all are contraindicated:
      1. Corticosteroid: High-potency corticosteroid (e.g., betamethasone, clobetasol)
         i. When located on the face or intertriginous areas only, low-potency corticosteroid (e.g., hydrocortisone) accepted
      2. Calcineurin inhibitor: tacrolimus ointment or pimecrolimus cream
      3. Vitamin D analog: calcipotriene cream/ointment or calcitriol ointment
      4. Retinoid: tazarotene cream

II. Tapinarof (Vtama) is considered investigational when used for all other conditions, including but not limited to:
   A. Plaque psoriasis in pediatric or adolescent patients
   B. Atopic dermatitis

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
    A. On first renewal: The member has exhibited improvement in extent and/or severity of psoriasis; **OR**
    B. Upon subsequent renewals: The member has exhibited continued improvement or stability in extent and/or severity of psoriasis; **AND**
III. If quantity requested is greater than 60 grams (1 tube) per 30-day supply, a quantity exception will be considered medically necessary when the following are met:
    A. Documentation of current body surface area affected by psoriasis; **AND**
    B. Rationale for need of more than one tube of cream per 30-days; **AND**
    C. Quantity requested does not exceed the amount needed to cover psoriatic lesions at a frequency of once daily.

Supporting Evidence

I. Tapinarof (Vtama) cream is a non-steroidal topical medication for the treatment of plaque psoriasis and has only been evaluated for safety and efficacy in adults for the treatment of plaque psoriasis. Coverage consideration is limited to those 18 years of age or older. It is being evaluated in pediatric patients in clinical trials, and use of therapy is best monitored in pediatrics and adolescents in a clinical trial setting until sufficient evidence for safety and efficacy in these populations is available.
II. Tapinarof (Vtama) cream is being evaluated in clinical trials for other skin conditions (e.g., atopic dermatitis); however, safety and efficacy have not been sufficiently demonstrated for any condition other than plaque psoriasis. Thus, coverage consideration is limited only to patients with a diagnosis of plaque psoriasis.
III. Tapinarof (Vtama) cream was evaluated as monotherapy in two Phase 3 clinical trials, which showed improvement in extent and severity of psoriasis as well as improvement in patient quality-of-life vs. a placebo vehicle. It was effective and well tolerated when used on the face and intertriginous areas. The extent of efficacy as well as safety when used in combination with other topical or systemic agents for this condition are currently unknown given the use as monotherapy only in clinical trials. Tapinarof (Vtama) cream joins a market of well-established, effective, and generic topical treatment options for psoriasis:
    - Topical corticosteroids (TCS) are the mainstay of therapy for plaque psoriasis, with a variety of chemical entities, potencies, and formulations to satisfy patient needs. These are highly effective, and safety concerns or adverse events can be mitigated by proper use (i.e., application to affected areas only), use of products that offer appropriate potency for extent/severity/area of the body, and the correct formulation (e.g., foams, sprays, oils, or shampoos for scalp involvement). Plaque psoriasis on the face or intertriginous areas may require a low potency TCS (e.g., OTC hydrocortisone 1%). Skin

atrophy is a common concern for utilizing TCS for extended durations of time; however, this is rarely a concern when TCS are applied to plaques appropriately (e.g., on active current lesions). For patients that experience quick recurrence of plaques after TCS discontinuation, TCS may be restarted intermittently, or steroid-sparing therapy may be considered, which may have synergistic effects with TCS.

- Topical calcineurin inhibitors (TCI): Tacrolimus 0.1% ointment and pimecrolimus 1% cream are the available generic TCI products, and they may be utilized as monotherapy or in combination with other topicals. These are safe and effective and have been evaluated for use on the face and intertriginous areas, as well as, in pediatric patients.
- Vitamin D analogs: Calcipotriene and calcitriol are the available generic products, and they may be utilized as monotherapy or in combination with other topicals. Combination use with TCS may have synergistic efficacy and increases tolerability vs. either agent alone. Monotherapy preparations are available, as well as betamethasone dipropionate-calcipotriene as a generic single preparation combination therapy as various formulations. These are applied once daily.
- Topical retinoid: Tazarotene 0.05% cream and 0.1% cream and foam are available with the 0.1% products being available as generics. Similar to vitamin D analogs, use with TCS may increase improve efficacy and tolerability. A single preparation combination therapy is available for halobetasol-tazarotene (Duobrii).

IV. Tapinarof (Vtama) cream has not proven to be superior in safety or efficacy to established therapies. Given the lack of definitive clinical advantage, as well as, higher cost relative to available generic therapies, use of at least three different classes of standard of care topical medications is required prior to coverage consideration of tapinarof (Vtama) cream.

V. One tube of tapinarof (Vtama) cream contains 60 grams, which should be adequate to cover 8% of the body surface area on average for 30-days when used appropriately (e.g., thin layer, once daily application). This quantity is likely sufficient for patients that have greater than 10% of the body surface area affected as well, given that when efficacy is realized the quantity needed to cover psoriatic plaques will decrease over time. Not all patients will respond to therapy or be able to tolerate therapy. Given these considerations, the plan's quantity limit for initial approval (i.e., first six months) is one tube per month, to minimize risk of medication waste as efficacy, tolerability, and adherence are realized. Upon renewal, a quantity exception may be granted based on medical necessity. The current body surface area affected and provider rationale for needing increased quantity will be reviewed relative to the labeled dosing recommendations and frequency. A one-time quantity exception may be granted when criteria are met. In clinical trials for patients that respond to therapy, tapinarof (Vtama) has the potential to treat psoriatic lesions and may prevent occurrence of new lesions for several months follow treatment success. If continuous use at excessive quantities of tapinarof (Vtama) cream are required, alternative treatment strategies with greater potential efficacy and favorable cost effectiveness may be more appropriate (e.g., other topical therapies, DMARDS, other systemic agents).

Investigational or Not Medically Necessary Uses

I. Tapinarof (Vtama) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Plaque psoriasis in pediatric or adolescent patients
   B. Atopic dermatitis

References

1. Lebwohl MG, Stein Gold L, Strober B, et al. Phase 3 trials of tapinarof cream for plaque psoriasis. N Engl J Med. 2021;385(24):2219-2229.
2. Elmets CA, Korman NJ, Prater EF, et al. Joint AAD–NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures. Journal of the American Academy of Dermatology. 2021;84(2):432-470.
3. Vtama [Prescribing Information]. Dermavant Sciences Inc. Long Beach, CA. May 2022.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
Chronic Inflammatory Disease Policy	Plaque psoriasis
Systemic Janus Associated Kinase Inhibitors in Chronic Inflammatory Disease Policy	Plaque psoriasis

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	08/2022

Policy Type: PA/SP Pharmacy Coverage Policy: UMP215

Description

Tasimelteon (Hetlioz, Hetlioz LQ) is an agonist of melatonin MT1 and MT2 receptors which are thought to be involved in the control of circadian rhythms.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
tasimelteon (Hetlioz)	20 mg capsules	Non 24-Hour Sleep-Wake Disorder; Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS)	30 capsules/30 days
tasimelteon (Hetlioz LQ)	4 mg/mL oral suspension	Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS)	0.7 mg/kg*
			158 ml bottle**

* for members weighing 28kg or less
** for members weighing more than 28kg

Initial Evaluation

I. Tasimelteon (Hetlioz, Hetlioz LQ) may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, a neurologist, sleep specialist, or psychiatrist; **AND**
   B. Treatment with melatonin (for at least three months continuously) has been ineffective, contraindicated, or not tolerated; **AND**
   C. A diagnosis of **Non-24-hour sleep-wake disorder (N24HSWD)** when the following are met:
      1. Member is 18 years of age or older; **AND**
      2. Member has a diagnosis of total blindness in both eyes without light perception; **AND**
      3. Provider has documented progressively shifting sleep-wake times with sleep diaries and/or actigraphy for at least 14 days; **AND**
      4. Treatment with at least TWO of the following groups has been ineffective or not tolerated, or **all** are contraindicated:
         i. benzodiazepines (eg. flurazepam, lorazepam, temazepam)
         ii. non-benzodiazepines (eg. doxepin, eszopiclone, zaleplon)
         iii. melatonin agonist (eg. ramelteon); **OR**

D. A diagnosis of **Nighttime sleep disturbances in Smith-Magenis Syndrome (SMS)** when the following are met:
    1. Genetic testing has identified a heterozygous deletion of 17p11.2; **OR**
        i. A heterozygous pathogenic variant involving RAI1; **AND**
    2. Request is for tasimelteon (Hetlioz) capsules; **AND**
        i. Member is 16 years of age or older; **OR**
    3. Request is for tasimelteon (Hetlioz LQ) oral solution; **AND**
        i. Member is between three and 15 years of age; **AND**
        ii. Current weight provided in documentation

II. Tasimelteon (Hetlioz, Hetlioz LQ) is considered investigational when used for all other conditions, including but not limited to:
    A. Sighted individuals with non-24-hour sleep-wake disorder
    B. Non-24-hour sleep-wake disorder in blind individuals with light perception
    C. Jet lag disorder
    D. Major depressive disorder

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms [e.g. longer duration of nighttime sleep, more alert during the day]

Supporting Evidence

I. The safety and efficacy of tasimelteon (Hetlioz) has been established in two phase III, placebo-controlled, randomized, double-blind studies (SET and RESET) in totally blind adult patients without light perception in both eyes and with a diagnosis of non-24-hour sleep-wake disorder.
    - Patients were randomized to receive tasimelteon 20mg or placebo every 24 hours at a fixed clock time one hour before target bedtime.
    - Primary outcome measure for the SET study of the proportion of entrained patients assessed in the intention-to-treat population assessed from 6-sulphatoxymelatonin (aMT6s) rhythms for 4 weeks starting from day 14, was met by eight (20%) of 40 patients in the tasimelteon group, compared with one (3%) of 38 patients in the placebo group.
    - Primary outcome measure for the RESET study of the proportion of maintenance of entrainment (aMT6s) has been met by nine (90%) of ten patients in the tasimelteon group, whereas only two (20%) of ten patients withdrawn to placebo, maintained entrainment.

- Entrained is the synchronization or alignment of the internal biological clock rhythm, including its phase and period, to external time cues, such as the natural dark-light cycle.
- Duration of nighttime sleep was improved by 28 minutes and the duration of daytime napping was reduced by 27 minutes, while each worsened when treatment was withdrawn.

II. There is a lack of randomized clinical trial data to show safety and efficacy of tasimelteon (Hetlioz) in pediatric patients with the diagnosis of N24SWD. Although the SMS indication is approved in pediatric patients – very few pediatric patients (N=11) have actually received the medication, thus, use for N24HSWD in those under 18 years of age would be considered experimental.

III. Per the American Academy of Sleep Medicine Clinical Practice Guideline, a diagnosis of N24SWD requires at least 14 days of documentation of progressively shifting sleep-wake times with sleep diaries and/or actigraphy.

IV. The exogenous melatonin (0.5-10 mg) has been shown to entrain the free-running circadian rhythms of some blind subjects. The American Academy of Sleep Medicine has identified three studies in their guideline. Melatonin was administered either one hour prior to preferred bedtime, or at a fixed clock hour (21:00), for a period of 26–81 days (one to three months). The entrainment rate (12 of 18) found in the current meta-analysis of melatonin treatment in N24SWD was 67%. Due to the lack of head-to-head trials there is no clinical trial data to show that one therapy is superior to the other.

V. The safety and efficacy of tasimelteon (Hetlioz) for Nighttime Sleep Disturbances in SMS has been established a pivotal phase 2/3, nine-week, double-blind, randomized, placebo-controlled, two-period crossover study in 14 adults and 11 pediatric patients.
- Patients 16 years of age and older received 20 mg capsules, and pediatric patients three years to 15 years of age received a weight-based dose of oral suspension.
- The primary endpoints in were nighttime total sleep time [assessed via daily diary total nighttime sleep duration (DDTST)] and nighttime sleep quality from a parent/guardian-recorded diary (DDSQ). The efficacy comparisons for nighttime sleep quality and total sleep time were based on the 50% of nights with the worst sleep quality and the 50% of nights with the least nighttime sleep in each 4-week period.
- Compared to placebo, treatment with tasimelteon (Hetlioz) resulted in a statistically significant improvement in the 50% worst nights' sleep quality. Although improvement on the 50% worst total nighttime sleep time numerically favored tasimelteon (Hetlioz) treatment, the difference was not statistically significant.

Primary Efficacy Measures	Treatment Group	LS Meana (SE)	Placebo-subtracted Difference (95% CI)
Average of 50% Worst Daily Nighttime Sleep Quality*	HETLIOZ (n=25)	2.8 (0.15)	0.4 (0.1, 0.7)
	Placebo (n=25)	2.4 (0.15)	-
Average of 50% Worst Daily	HETLIOZ (n=25)	7.0 (0.26)	0.3 (-0.0, 0.6)
	Placebo (n=25)	6.7 (0.26) -	-

Nighttime Total Sleep Time, hours			

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval unadjusted for multiplicity.
[a] LS Means are the model-based averages based on the 50% worst days per 4-week period.
[b] Difference (drug minus placebo) in least-squares means.
* Endpoint on which HETLIOZ was statistically significant different from placebo after controlling for multiple comparisons.

VI. The recommended dosage of tasimelteon (Hetlioz LQ) oral suspension for the treatment of nighttime sleep disturbance in SMS pediatric patients three to 15 years of age is by body weight. For patients with 28 kg or less the recommended dose is 0.7 mg/kg and for patients who weigh more than 28kg the recommended dose is 20 mg one hour before bedtime.

VII. Smith-Magenis syndrome (SMS) is a developmental disorder that affects many parts of the body. The major features of this condition include mild to moderate intellectual disability, delayed speech and language skills, distinctive facial features, sleep disturbances, and behavioral problems. Most people with SMS have a deletion of genetic material in each cell from a specific region of chromosome 17. Although this region contains multiple genes, researchers believe that the loss of one particular gene, RAI1, is responsible for most of the features of the condition. In most of these cases, the deletion is not inherited, occurring randomly during the formation of eggs or sperm, or in early fetal development.

- The diagnosis of SMS is established in a proband with suggestive clinical features and one of the following on molecular genetic testing: A heterozygous deletion of 17p11.2 or heterozygous pathogenic variant involving RAI1. When the phenotypic findings suggest the diagnosis of SMS, molecular genetic testing approaches can include chromosomal microarray analysis, single-gene testing, or use of a multigene panel.

VIII. Recent studies have attributed the sleep disturbance in SMS to a primary disturbance of the circadian clock, with RAI1 functioning as a positive regulator of Circadian Locomotor Output Cycles Kaput (CLOCK) transcription, a key component of the mammalian circadian oscillator. Additionally, disrupted melatonin secretion has been noted with moderate to high levels of daytime salivary melatonin observed in SMS patients.

IX. As patients with SMS typically display a diurnal rather than nocturnal peak in melatonin secretion, exogenous melatonin has been used nocturnally to supplement the typical biological melatonin secretion. By adding an exogenous melatonin dose prior to bedtime, a nocturnal rise in melatonin levels can assist in increasing the biological propensity to sleep. Given the very limited experience of tasimelteon (Hetlioz) in pediatric populations, the safety and efficacy profile are largely unknown. Melatonin has a more established safety and efficacy profile and should be considered for use prior to tasimelteon (Hetlioz).

Investigational or Not Medically Necessary Uses

I. Tasimelteon (Hetlioz) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Sighted individuals with non-24-hour sleep-wake disorder and non-24-hour sleep-wake disorder in blind individuals with light perception
      i. There no published clinical trial data to show safety and efficacy and support the use of tasimelteon (Hetlioz) in these patient populations.
   B. Jet lag disorder

i. A phase II, randomized, double blind proof of concept study to evaluate the effects of tasimelteon and placebo in travelers with jet lag disorder with the primary outcome measure of changes in sleep after transmeridian travel measured by nighttime sleep parameters
ii. A randomized, double-blind, placebo-controlled, parallel design study evaluating the effects of tasimelteon compared to placebo on jet lag type insomnia enrolled 320 healthy adult patients. Tasimelteon treatment increased Total Sleep Time in the first 2/3 of the night (primary endpoint) by 60.3 min (95%CI 44.0 to 76.7, P < 0.0001) and whole night TST by 85.5 min (95% CI 64.3 to 106.6, P < 0.0001), improved next day alertness, next day sleepiness, and shortened latency to persistent sleep by −15.1 min (95% CI −26.2 to −4.0, P = 0.0081).
iii. Jet Lag was induced by an immediate phase advance of the sleep-wake cycle in a sleep clinic, rather than jet travel in the eastward direction.
iv. There isn't robust safety and efficacy data to support the use of tasimelteon (Hetlioz) in the treatment of the jet lag disorder.

C. Major Depressive Disorder (MDD)
i. A randomized, parallel, double-masked, placebo-controlled, multicenter outpatient study comparing tasimelteon with placebo with 507 enrolled participants (MAGELLAN) followed by a 52-week open label extension.
- The primary outcome measure was change from baseline to endpoint at week 8 using the total score of Hamilton Depression Rating Scale (HAM-D) was not met.
- The clinical trial showed insufficient efficacy and limited safety data.

References

1. Hetlioz [Prescribing Information]. Washington, D.C. Vanda Pharmaceuticals Inc. October 2019.
2. Lockley SW, et al. Tasimelteon for non-24-hour sleep-wake disorder in totally blind people (SET and RESET): two multicentre, randomised, double-masked, placebo-controlled phase 3 trials. *Lancet*. 2015;386(10005):1754-1764. doi:10.1016/S0140-6736(15)60031-9
3. R. Robert Auger, MD, et al. Clinical Practice Guideline for the Treatment of Intrinsic Circadian Rhythm Sleep-Wake Disorders: Advanced SleepWake Phase Disorder (ASWPD), Delayed Sleep-Wake Phase Disorder (DSWPD), Non-24-Hour Sleep-Wake Rhythm Disorder (N24SWD), and Irregular Sleep-Wake Rhythm Disorder (ISWRD). An Update for 2015. J Clin Sleep Med. 2015 Oct 15; 11(10): 1199–1236.
4. Brandon Peters, MD. Overview of Entrainment of Circadian Rhythms in Sleep. VeryWellhealth. 2020. https://www.verywellhealth.com/what-is-entrainment-of-circadian-rhythms-in-sleep-3014883
5. Hack, L. M. et al. The effects of low-dose 0.5-mg melatonin on the free-running circadian rhythms of blind subjects. J Biol Rhythms. 2003;18(5):420-429. doi:10.1177/0748730403256796
6. Vanda Pharmaceuticals. Melatonin Agonist Effects of Tasimelteon Versus Placebo in Patients With Major Depressive Disorder (MAGELLAN). ClinicalTrials.gov Identifier: NCT01428661
7. Brian J. Shayota, et al. Behavior and Sleep Disturbance in Smith-Magenis Syndrome. Curr Opin Psychiatry. 2019 Mar; 32(2): 73–78. doi: 10.1097/YCO.0000000000000047
8. Kaplan KA, Elsea SH, Potocki L. Management of Sleep Disturbances Associated with Smith-Magenis Syndrome. CNS Drugs. 2020;34(7):723-730. doi:10.1007/s40263-020-00733-5
9. Vanda Pharmaceuticals. A Proof of Concept Study to Evaluate the Effects of Tasimelteon and Placebo in Travelers With Jet Lag Disorder. ClinicalTrials.gov Identifier: NCT03291041

10. Polymeropoulos CM, Mohrman MA, Keefe MS, et al. Efficacy of Tasimelteon (HETLIOZ®) in the Treatment of Jet Lag Disorder Evaluated in an 8-h Phase Advance Model; a Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. Front Neurol. 2020;11:611. Published 2020 Jul 9. doi:10.3389/fneur.2020.00611
11. Vanda Pharmaceuticals. Melatonin Agonist Effects of Tasimelteon Versus Placebo in Patients With Major Depressive Disorder (MAGELLAN). ClinicalTrials.gov Identifier: NCT01428661
12. NIH Genetics and Rare Diseases (GARD). Smith-Magenis syndrome. https://rarediseases.info.nih.gov/diseases/8197/smith-magenis-syndrome
13. Smith ACM, Boyd KE, Elsea SH, et. al. Smith-Magenis Syndrome. GeneReviews. June 28, 2012; https://www.ncbi.nlm.nih.gov/books/NBK1310/.
14. Smith Magenis Syndrome. NORD. 2017; https://rarediseases.org/rare-diseases/smith-magenis-syndrome/.

Policy Implementation/Update:

Action and Summary of Changes	Date

• Added new indication of Nighttime Sleep Disturbances in SMS
• Added a new formulation, the tasimelteon (Hetlioz LQ) oral solution
• New criteria added for the indication of N24HSWD:
  ○ Treatment with melatonin (for at least three months continuously) has been ineffective, contraindicated or not tolerated
  ○ Member has a diagnosis of total blindness in both eyes without light perception
  ○ Provider has documented progressively shifting sleep-wake times with sleep diaries and/or actigraphy for at least 14 days
  ○ Treatment with at least TWO alternatives has been ineffective or not tolerated, or all are contraindicated: benzodiazepines (eg. flurazepam, lorazepam, temazepam), or non-benzodiazepines (eg. doxepin, eszopiclone, zaleplon) or melatonin agonist (eg. ramelteon)
• Criteria removed from the indication of N24HSWD:
  ○ Member has no hepatic impairment or mild to moderate hepatic impairment
  ○ Member is not on concurrent strong CYP3A4 inducers or CYP1A2 inhibitors
Criteria updated to policy format
	12/2020

Criteria created	04/2014

Policy Type: PA/SP Pharmacy Coverage Policy: UMP184

Split Fill Management*

Description

Tazemetostat (Tazverik) is an orally administered inhibitor of methyltransferase, EZH2.

Length of Authorization

- N/A

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
tazemetostat (Tazverik)	200 mg tablets	Epithelioid sarcoma, advanced or metastatic, not eligible for resection; Follicular lymphoma, relapsed or refractory, EZH2 mutation-positive, in that that have received at least two therapies; Follicular lymphoma, relapsed or refractory, in those with no satisfactory alternative therapy	240 tablets/30 days

Initial Evaluation

I. Tazemetostat (Tazverik) is considered investigational when used for all conditions, including but not limited to:
   A. Epithelioid sarcoma
   B. Non-Hodgkin lymphoma, including follicular lymphoma

Renewal Evaluation

I. N/A

Supporting Evidence

I. Background: Epithelioid sarcoma is a very rare cancer of the soft tissue, generally seen in younger populations (average age of 27). This aggressive condition is known for recurrence, spread to locoregional lymph nodes, and eventually distant metastases. Common sites of origin include fingers, hands, forearms, feet, and other limbs. First-line management is typically surgery, with local recurrence necessitating amputation in many cases. Although, not specifically FDA-approved for epithelioid sarcoma, there are several systemic therapies used in the metastatic setting. Often, anthracycline based regimens (e.g., doxorubicin with or without ifosfamide), gemcitabine, pazopanib (Votrient), doxetaxel, sunitinib (Sutent), dacarbazine, epirubicin, and temozolomide.

II. Efficacy: Tazemetostat (Tazverik) was approved on data from a Phase 2 trial. Pooled data from two cohorts, five and six (n=62, n=44), were used to support the approval. Seventy-seven percent of patients had prior surgery and 61% had prior chemotherapy. Primary outcomes included objective response rate (ORR) assessed every eight weeks and progression-free survival (PFS). Secondary endpoints were duration of response (DOR), disease control rate (DCR) and overall survival (OS). The pooled data showed an objective response rate of 13% (CR 1.6%, PR 11%). Duration of response was 12.8 months (3.5-24 months). Pooled data for progression-free survival (PFS), disease control rate (DCR) and overall survival (OS) were not reported for the pooled data; however, for Cohort 5 PFS was 23.7 weeks, DCR was 21%, and OS was 82 weeks.

III. Safety: There are no contraindications for tazemetostat (Tazverik); however, there is a warning for development of secondary malignancies, such as T-cell lymphoblastic lymphoma, myelodysplastic syndrome, and acute myeloid leukemia. Six out of 668 treated patients had developed secondary malignancy as of quarter May 2019. Common (≥ 20%) adverse reactions noted from the trial included: fatigue, nausea, decreased appetite, vomiting and constipation. One patient in the clinical trial discontinued therapy due to adverse events, 34% required a dose interruption, and there were not deaths from treatment. Tazemetostat (Tazverik) has significant drug interactions with CYPP450 inhibitors and inducers, and there is a warming for embryo fetal toxicity and lactation. Due to the limited number of subjects treated and short duration of use, the safety profile of tazemetostat (Tazverik) is largely unknown at this time.

IV. The quality of the evidence is low given the Phase 2, open-label, single-arm trial. The primary endpoints have not been correlated with clinically meaningful outcomes such as improvement in morbidity, mortality or symptom relief, and results have not been confirmed in other studies. Additionally, due to the limited number of subjects treated, the safety profile is highly unknown. Coupled with the low rates of response, there is uncertain usefulness of tazemetostat (Tazverik) at this time.

V. Tazemetostat (Tazverik) was approved under the accelerated approval pathway and orphan drug designation. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials.

VI. Follicular lymphoma (FL), is an indolent form of NHL that arises from B-lymphocytes. Treatment is dependent on stage, or histologic grade of condition, and may include the following: radiation therapy, immunotherapy, and chemotherapy. In the space of relapsed or refractory to two prior therapies, the PI3K inhibitors are recommended per NCCN (e.g., copanlisib, duvelisib, idelalisib), as well as selinexor.

VII. Tazemetostat (Tazverik) for FL was evaluated for safety and efficacy in one open-label, single-arm, Phase 2 trial at 800 mg twice daily. There were 99 patients included in the trial , 45 of which were EZH2 mutated, and 54 were EZH2 wild type. Patients were adults with confirmed FL (grade 1-3b), relapsed or refractory to two or more standard systemic therapies, with life expectancy of three months or more, and adequate organ function. Some patients had up to five or more previous therapies, and up to 59% were rituximab refractory, up to 28% were double refractory, and up to 29% had hematopoietic stem cell transplant.

VIII. Tazemetostat (Tazverik) was approved under the accelerated approval pathway for FL based on objective response rate, duration or response, and progression free survival. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials. Treatment emergent adverse events (TEAE) occurred in 99% of patients, and serious AE occurred in 27%. The most common serious AE being sepsis, physical health deterioration, and anemia. Other notable serious AE were neutropenia, pancytopenia, global amnesia, arrhythmia, and myelodysplastic syndrome. Dose reductions due to adverse events as well as dose interruptions occurred at rates of 27%, and 8% of patients permanently discontinued due to AE. One case of AML was reported, and four patients died within 30 days of the last dose of study drug. The study investigators deemed these not related to treatment.

IX. Given the observational nature of the data, true medication safety and efficacy is unknown. Open-label, single-arm trials are insufficient for determining cause and effect of treatment. Additionally, ORR, DoR, and PFS have not been correlated with clinically meaningful outcomes such as improvement in quality of life, symptom control, or overall survival.

Investigational or Not Medically Necessary Uses

I. There is a lack of high-quality data from randomized controlled trials to indicate the safety and efficacy of tazemetostat (Tazverik) in the following indications:
   A. Soft tissue sarcoma, including epithelioid sarcoma
   B. Non-Hodgkin lymphoma, including follicular lymphoma
   C. Other types of lymphoma, including but not limited to mediastinal, B-Cell, Mantle-Cell, Marginal Zone,
   D. Rhabdoid tumors
   E. Mesothelioma
   F. Kidney, bladder, urothelial cancers
   G. Hepatocellular carcinoma

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Tazverik [Prescribing Information]. Epizyme, Inc. Cambridge, MA. July 2020.
2. Morschhauser F., Tilly H., Chaidos A., et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicenter, phase 2 trial. *Lancet Oncol.* 2020 Nov;21(11): 1433-1442. PMID 33035457.
3. National Comprehensive Cancer Network. NCCN Guidelines: Treamtn of B-Cell Lymphomas. Version 4.2020, updated August 2020.
4. ClinicalTrials.gov, Available at https://clinicaltrials.gov/ct2/results?cond=&term=tazemetostat&cntry=&state=&city=&dist=. Accessed February 2020. Tazverik [Prescribing Information]. Epizyme, Inc. Cambridge, MA. January 2020.
5. National Comprehensive cancer Network. NCCN Guidelines: Soft Tissue Sarcoma. Version 6.2019. Available at https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/PDF/sarcoma.pdf. February 2020.
6. U.S. National Library of Medicine. A phase II, multicenter study of the EZH2 inhibitor tazemetostat in adult subjects with INI1-negative tumors or relapsed/refractory synovial sarcoma. Available at https://clinicaltrials.gov/ct2/show/NCT02601950?term=NCT02601950&draw=2&rank=1. Accessed February 2020.
7. U.S. Food & Drug Administration. FDA approved tazemetostat for advanced epithelioid sarcoma. Available at https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tazemetostat-advanced-epithelioid-sarcoma. January 24, 2020.
8. Sobanko JF, Meijer L, Nigra TP. Epithelioid sarcoma: a review and update. *J Clin Aesthet Dermatol*. 2009;2(5):49-54.
9. Frezza AM, Jones RL, Lo vullo S, et al. Anthracycline, gemcitabine, and pazopanib in epithelioid sarcoma: A multi-institutional case series. *JAMA Oncol*. 2018;4(9):e180219.
10. Jones RL, Constantinidou A, Olmos D, et al. Role of palliative chemotherapy in advanced epithelioid sarcoma. *Am J Clin Oncol*. 2012;35(4):351-7.

Policy Implementation/Update:

Action and Summary of Changes	Date
Indication of Follicular Lymphoma reviewed and supporting evidence added to policy	01/2021
Policy created	05/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP024

Description

Teduglutide (Gattex) is a subcutaneously administered recombinant synthetic glucagon like peptide 2 (GLP-2) analog.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
teduglutide (Gattex)	5 mg vial kit (one vial)	Short Bowel Syndrome (SBS)	1 vial/1 day	177513
	5 mg vial kit (30 vial)		30 vials/30 days	

Initial Evaluation

I. Teduglutide (Gattex) may be considered medically necessary when the following criteria below are met:
   A. Member is one year of age or older and weighs more than 10 kg; **AND**
   B. Teduglutide (Gattex) has been prescribed by, or consultation with a specialist in gastroenterology; **AND**
   C. A diagnosis of **Short Bowel Syndrome**; **AND**
      1. Member dependence on parenteral nutrition/intravenous support for at least 12 months; **AND**
      2. Member dependence on parenteral nutrition at least three times a week; **AND**
      3. Laboratory assessment within the last six months of bilirubin, alkaline phosphatase, lipase and amylase to rule out gallbladder, biliary tract or pancreatic disease; **AND**
      4. Colonoscopy within the last 6 months to rule out colorectal polyps or small bowel neoplasia in adult members; **OR**
      5. Fecal occult blood testing in children and adolescents within the last 6 months; **AND**
         i. Documentation of a follow-up colonoscopy for any positive fecal occult blood test

II. Teduglutide (Gattex) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:

A. Crohn's disease
B. Enterocutaneous Fistula (ECF)
C. Gastric emptying

Renewal Evaluation

I. Clinical documentation of response to therapy as demonstrated by:
   A. Decrease in volume of parenteral or intravenous nutritional support; **OR**
   B. Decrease in number of days of parenteral or intravenous nutritional support; **AND**
II. Colonoscopy performed within the last 12 months to rule out colorectal polyps or small bowel neoplasia upon first renewal, and, no less than every five years; **AND**
III. Bilirubin, alkaline phosphatase, lipase, and amylase laboratory assessment to rule out gallbladder, biliary tract or pancreatic disease within the last six months.

Supporting Evidence

I. Teduglutide (Gattex) is FDA approved for treatment adults and pediatric patients 1 year of age or older with Short Bowel Syndrome (SBS) who are dependent on parenteral support.
II. The pivotal trial included patients with SBS who were dependent on parenteral nutrition/intravenous support for at least 12 months and at least 3 times per week.
III. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for an increased dosing frequency. The higher dose treatment arm did not demonstrate a statistically significant difference when compared to placebo.
IV. Colonoscopies should be completed again 1 year after treatment then no less frequently than every 5 years to evaluate for polyps and gastrointestinal malignancies.
V. Lab assessments are recommended every 6 months to evaluate for gallbladder, biliary tract and pancreatic disease.

Investigational or Not Medically Necessary Uses

I. Crohn's Disease
   A. Phase II clinical trials have evaluated teduglutide for the treatment of Crohn's disease.
   B. Clinical concerns for the safety of teduglutide in patients with Crohn's disease include neoplastic growth, intestinal obstruction and biliary and pancreatic disease.
   C. Large, well-controlled clinical trials are needed to demonstrate benefit of use of teduglutide in patients with Crohn's Disease.
II. Clinical trials are ongoing in the following indications:
   A. Enterocutaneous Fistula (ECF)
   B. Gastric emptying

References

1. Gattex [Prescribing Information]. Bedminister, NJ: NPS Pharmaceutical; June 2019.
2. Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B, O'Keefe SJ. Randomized placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. Gut. 2011 Jul;60(7):902-14

Policy Implementation/Update:

Date Created	May 2013
Date Effective	May 2013
Last Updated	August 2013
Last Reviewed	05/2013, 09/2013, 06/2019

Action and Summary of Changes	**Date**
Created new policy format. Addition of new FDA approved indication in pediatric population.	06/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP087

Description

Tegaserod (Zelnorm) is an orally administered serodonin-4 (5-HT4) receptor agonist.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
tegaserod (Zelnorm)	6 mg tablets	Irritable bowel syndrome with constipation	60 tablets/30 days

Initial Evaluation

I. Tegaserod (Zelnorm) may be considered medically necessary when the following criteria below are met:
   A. The member is between 18 and 65 years of age; **AND**
   B. The medication is prescribed by, or in consultation with, a gastroenterologist; **AND**
   C. A diagnosis of **irritable bowel syndrome with constipation (IBS-C)** when the following are met:
      1. The member is female; **AND**
      2. The member does not have current, or historical, cardiovascular disease; **AND**
      3. The member has had an inadequate response to the ALL of the following, unless all are contraindicated:
         i. Dietary modifications (e.g., removal of offending foods, increased fiber intake) AND increased physical activity; **AND**
         ii. At least one osmotic laxative (e.g., polyethylene glycol); **AND**
         iii. Plecanatide (Trulance); **AND**
         iv. Linaclotide (Linzess); **AND**
         v. Lubiprostone (Amitiza)

II. Tegaserod (Zelnorm) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Irritable bowel syndrome with constipation in males

III. Tegaserod (Zelnorm) is considered investigational when used for all other conditions, including but not limited to:
   A. Idiopathic chronic constipation

B. Opioid or other drug induced constipation
C. Gastroesophageal reflux disease (GERD)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. The member is between 18 and 65 years of age; **AND**
IV. The medication is prescribed by, or in consultation with, a gastroenterologist; **AND**
    A. **A diagnosis of irritable bowel syndrome with constipation (IBS-C)**; **AND**
        1. The member does not have a history of, or current cardiovascular disease; **AND**
        2. The member has experienced a response to treatment (e.g. increase in rate of bowel movements)

Supporting Evidence

I. Tegaserod (Zelnorm), a serotonin-4 (5-HT4) receptor agonist, is FDA-approved and indicated for the treatment of irritable bowel syndrome with constipation (IBS-C) in women < 65 years of age. It was originally approved in 2002, for short-term treatment of women with IBS-C; however, it was withdrawn from the market in 2007 due to an unfavorable cardiovascular (CV) and suicidal ideation and behavior (SI/B) safety profile.
II. Efficacy to support reintroduction of tegaserod (Zelnorm) was based on evidence established at the time of original approval and no new evidence on efficacy has been added. Tegaserod (Zelnorm) was evaluated in three multicenter, double-blind, placebo-controlled, 12-week trials of 2,470 women that had at least a three-month history of IBS-C. Response rate (RR) was the primary outcome, and was based on subjective response on a five parameter scale measured each week indicating: completely relieved, considerably relieved, somewhat relieved, unchanged, or worse. Tegaserod (Zelnorm) had superior response rates compared to placebo ranging from 6 to 28%. Secondary outcomes of pain, discomfort and bloating were evaluated on a six-to-seven-point intensity scale. Positive response, defined as at least a 1-point reduction, was measured to be 1-10% superior for tegaserod (Zelnorm) for abdominal pain or discomfort and 4-11% for bloating. The baseline bowel movement rate averaged 3.8 per week and increased to 6 per week for tegaserod (Zelnorm) and 5.5 for placebo.
III. During clinical trials, responders were defined as participants with complete relief or considerable relief for at least two of the four weeks, or somewhat relieved for all of the four weeks (after one month of treatment). It is recommended to assess response to treatment after four to six weeks of treatment, and to discontinue tegaserod (Zelnorm) for nonresponsive patients.
IV. Tegaserod (Zelnorm) is contraindicated in those with established CV history (specifically, myocardial infarction, stroke, transient ischemic attach, angina), renal impairment, hepatic impairment, bowel obstruction, gallbladder disease, suspected sphincter of Oddi dysfunction, or

abdominal adhesions. Warnings and precautions include CV ischemic events, major adverse CV events (MACE), ischemic colitis, volume depletion with diarrhea, and SI/B. Common adverse effects (≥ 2%) include headache, abdominal pain, nausea, diarrhea, flatulence, dyspepsia, and dizziness. Approval of tegaserod (Zelnorm) reintroduction was supported by a complete safety review by the FDA and FDA-assembled Gastrointestinal Drugs Advisory Committee (GIDAC). Retrospective analyses of pooled data from 18,645 patients in 29 placebo-controlled trials in various disease states of at least four weeks duration were included. The imbalance in CV events was measured to be 0.1% for tegaserod (Zelnorm) versus 0.01% in placebo. There was one death, attributed to suicide, during the trial; although, the member had a history of mild depression. The rate of SI/B is measured to be 0.07% for tegaserod (Zelnorm) vs. 0.02% for placebo.

V. First-line treatment options for the treatment of IBS-C include dietary modifications, increased fiber intake, and physical activity. Adjunctive pharmacotherapy includes over-the-counter osmotic laxatives. When lifestyle modifications and osmotic laxatives fail to produce sufficient relief of constipation, further pharmacological interventions are indicated. The 2021 American College of Gastroenterology (ACG) clinical guidelines for management of IBS recommend use of guanylate cyclase activators (e.g. linaclotide [Linzess], plecanatide [Trulance]) and chloride channel activator (e.g. lubiprostone [Amitiza]) as recommended therapeutic options based on high and moderate quality of clinical evidence, respectively. Tegaserod (Zelnorm) may be considered a subsequent-line therapy based on a conditional recommendation (low quality of evidence) from ACG review panel. Thus, due to the limited efficacy and concerning safety profile, tegaserod (Zelnorm) should only be reserved for those that have exhausted other treatment options.

Investigational or Not Medically Necessary Uses

I. Irritable bowel syndrome with constipation (IBS-C) in males
   A. Two randomized, placebo-controlled, double-blind trials of 288 men did not show differences in efficacy of tegaserod (Zelnorm) versus placebo. This information is stated in the product labeling.

II. Clinical trials are underway, but have not yet been completed to provide insight to safety and efficacy of tegaserod (Zelnorm) in the following settings:
   A. Idiopathic chronic constipation
   B. Opioid or other drug induced constipation
   C. Gastroesophageal reflux disease (GERD)

References

1. Zelnorm [Prescribing Information]. Sloan Pharma/WorldMeds LLC. Louisville, KY. 2019.
2. Black CJ, Burr NE, Ford AC. Relative Efficacy of Tegaserod in a Systematic Review and Network Meta-analysis of Licensed Therapies for Irritable Bowel Syndrome with Constipation. Clin Gastroenterol Hepatol. 2019.
3. Vakil N, Laine L, Talley NJ, et al. Tegaserod treatment for dysmotility-like functional dyspepsia: results of two randomized, controlled trials. Am J Gastroenterol. 2008;103(8):1906-19.
4. Weinberg D.S., Smalley W. Heidelbaugh J.J., et al. American Gastroenterological Association institute guidelines on the pharmacological management of irritable bowel syndrome. Gastroenterology. 2014;144: 1146-1148.
5. Chandar AK. Diagnosis and treatment of irritable bowel syndrome with predominant constipation in the primary-care setting: focus on linaclotide. Int J Gen Med. 2017;10:385-393.

6. FDA Joint Meeting of the Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee Briefing Document; Sloan Pharma; US WorldMeds, 10/17/2018; accessed via https://www.fda.gov/media/119013/download
7. Lacy BE, Pimentel M, Brenner DM, Chey WD, Keefer LA, Long MD, Moshiree B. ACG Clinical Guideline: Management of Irritable Bowel Syndrome. Am J Gastroenterol. 2021 Jan 1;116(1):17-44.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy updated to require trials of Trulance, Linzess, AND Amitiza for coverage consideration of Zelnorm; updated supporting evidence to reflect 2021 ACG guideline recommendations; made minor formatting changes to align policy with current format; **(Effective 7/1/2021)**	05/2021
Policy created	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP155

Description

Telotristat ethyl (Xermelo) is an orally administered tryptophan hydroxylase inhibitor indicated for the treatment of carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
telotristat ethyl (Xermelo)	250 mg tablets	Carcinoid Syndrome Diarrhea	84 tablets/28 days

Initial Evaluation

I. Telotristat ethyl (Xermelo) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, oncologist or gastroenterologist; **AND**
   C. Telotristat ethyl (Xermelo) will be used in combination with a somatostatin analog therapy (e.g., octreotide [Sandostatin/Sandostatin LAR depot], lareotide [Somatuline depot]); **AND**
   D. A diagnosis of **carcinoid syndrome diarrhea** when the following are met:
      1. Clinical documentation of significant diarrhea (≥ 4 bowel movements per day on average); **AND**
      2. Treatment with a somastatin analog therapy (e.g. octreotide [Sandostatin/Sandostatin LAR depot], lareotide [Somatuline depot]) has not been effective after at least 3 months of therapy, was not tolerated, or is contraindicated.

II. Telotristat ethyl (Xermelo) is considered investigational when used for all other conditions, including but not limited to:
   A. Carcinoid syndrome without diarrhea
   B. Biliary Tract Cancer
   C. Pancreatic Cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms defined by a decrease in overall average bowel movements per week from baseline; **AND**
IV. Telotristat ethyl (Xermelo) will be used in combination with a somatostatin analog therapy (e.g., octreotide [Sandostatin/Sandostatin LAR depot], lareotide [Somatuline depot]).

Supporting Evidence

I. The safety and efficacy for telotristat ethyl (Xermelo) was studied in a 12-week double-blind, placebo-controlled, randomized, multicenter trial in adult patients with well differentiated metastatic neuroendocrine tumor and carcinoid syndrome diarrhea who were having between 4 to 12 daily bowel movements despite the use of SSA therapy at a stable dose for at least 3 months. The primary efficacy outcome was the change from baseline in the number of daily bowel movements averaged over the 12-week treatment period; in the telotristat ethyl (Xermelo) arm, there was a reduction of -1.4 bowel movements per day compared to -0.6 in the placebo arm with $p<0.001$.

Investigational or Not Medically Necessary Uses

I. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for the following indications:
   A. Carcinoid syndrome without diarrhea
   B. Biliary Tract Cancer
   C. Pancreatic Cancer/Other Neuroendocrine Tumors (NETs)

References

1. Xermelo [Prescribing Information]. Woodlands, TX: Lexicon Pharmaceuticals, Inc. February 2017.
2. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines®): Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors). Version 1.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine_blocks.pdf

Policy Implementation/Update:

Date Created	11/2019
Date Effective	December 2019
Last Updated	
Last Reviewed	

Action and Summary of Changes	Date

temozolomide (Temodar®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP163

Description

Temozolomide is an alkylating agent that undergoes rapid nonenzymatic conversion to the reactive compound 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC). The cytotoxicity of MTIC is thought to be caused primarily by alkylation of DNA. Alkylation (methylation) occurs mainly at the O^6 and N^7 positions of guanine which leads to DNA double strand breaks and apoptosis.

Length of Authorization

- Initial: Three months
- Renewal: Six months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
temozolomide (Temodar)	5 mg capsules	All indications	Maximum 200 mg/m^2/day
	20 mg capsules		
	100 mg capsules		
	140 mg capsules		
	180 mg capsules		
	250 mg capsules		
Provider Administered Agents*			
temozolomide (Temodar)	100 mg vial	All indications	Maximum 200 mg/m^2/day

**Medical drug that requires administration by a healthcare professional and is not available for self-administration by the member, considered one of the excluded classes under the prescription benefit.*

Initial Evaluation

I. Temozolomide (Temodar) may be considered medically necessary when treatment with generic temozolomide has been ineffective, contraindicated, or not tolerated.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread.

References

1. Temodar (temozolomide) [Prescribing Information]. Whitehouse Station, NJ: Merck & Co. October 2017.

Policy Implementation/Update:

Action and Summary of Changes	Date
• Removed generic temozolomide from the policy • Removed indication-specific criteria	03/2020
Updated to policy format	12/2019
Previous reviews	03/2016
Policy created	05/2012

Policy Type: PA/SP Pharmacy Coverage Policy: UMP170

Description

Tenapanor (e.g., Ibsrela, Xphozah) is an orally administered sodium/hydrogen exchange 3 (NHE3) inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
tenapanor (Ibsrela)	Irritable bowel syndrome with constipation (IBS-C)	50 mg tablets	60 tablets/30 days
tenapanor (Xphozah)	Reduction of serum phosphorus in adults with chronic kidney disease (CKD) on dialysis as add-on therapy in patients who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy	10 mg tablets	60 tablets/30 days
		20 mg tablets	
		30 mg tablets	

Irritable bowel syndrome with constipation (IBS-C)

Initial Evaluation

I. **Tenapanor (Ibsrela)** may be considered medically necessary when the following criteria below are met:
   A. The member is 18 years of age or older; **AND**
   B. The medication is prescribed by, or in consultation with, a gastroenterologist; **AND**
   C. A diagnosis of **irritable bowel syndrome with constipation (IBS-C)** when the following are met:
      1. The member has had an inadequate response, or intolerance to, all of the following, unless all are contraindicated (*Please note: These agents may be subject to additional prior authorization review):
         i. Dietary and lifestyle modifications (e.g., removal of offending foods, increased fiber intake) and increased physical activity; **AND**
         ii. At least one osmotic laxative (e.g., polyethylene glycol); **AND**
         iii. Plecanatide (Trulance); **AND**
         iv. Lubiprostone or Amitiza*; **AND**
         v. Linaclotide (Linzess)*

II. Tenapanor (Ibsrela) is considered investigational when used for all other conditions, including but not limited to:
   A. Hyperphosphatemia
   B. Chronic kidney disease
   C. Irritable bowel syndrome with diarrhea
   D. Mixed irritable bowel syndrome
   E. Chronic idiopathic constipation
   F. Opioid-induced constipation

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has a diagnosis of irritable bowel syndrome with constipation (IBS-C); **AND**
IV. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in complete spontaneous bowel movements per week from baseline, reduction in abdominal pain)

Supporting Evidence

I. Tenapanor (Ibsrela) is approved by the US Food and Drug Administration (US-FDA) for the treatment of irritable bowel syndrome with constipation (IBS-C) in adults.
II. Given the complexities involved in diagnosis and management of IBS-C, as well as required monitoring for adverse events and therapy response, therapy decisions regarding initiation of tenapanor (Ibsrela) must be made by, or under the supervision of, a specialist practicing in this setting (e.g., gastroenterologist).
III. Tenapanor (Ibsrela) is a sodium/hydrogen exchange 3 (NHE3) inhibitor acting specifically in the GI tract, with minimal systemic availability following oral administration. Inhibition of NHE3 leads to a reduction in dietary sodium absorption and an increase in intracellular protons across membranes in the GI tract, which results in reduction of phosphate absorption from the small intestine and colon. Additionally, consequent increase in sodium and phosphorus content in the stool, decreased urinary sodium and phosphorus excretion, and increased water secretion into the intestinal lumen and the increased stool water content leads to loosened stool consistency and increased bowel movement frequency.
IV. Tenapanor (Ibsrela) has a Black Box Warning for serious dehydration in pediatric patients and has not been evaluated in any pediatric population to date. It is contraindicated in those less than six years of age and comes with a recommendation to avoid use in those less than 12 years of age due to animal studies showing cause of death to be dehydration in young juvenile rats. Additionally, tenapanor (Ibsrela) is also contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.
V. **Irritable Bowel Syndrome with Constipation (IBS-C):** Tenapanor (Ibsrela) was evaluated in two double-blind, placebo-controlled, randomized trials in adult patients –T3MPO-2 and T3MPO-1. The majority of subjects were female (83%), white, and all met Rome III criteria for IBS-C. This

requires a pain score of at least three on a 0-10 scale, less than three complete spontaneous bowel movements (CSBMs) per week, and less than five spontaneous bowel movements (SBMs) per week.

- The primary outcome was proportion of responders, defined as achieving both of the following for at least six of the first 12 weeks of the trials: an increase of at least one CSBM per week on average and a reduction of 30% in weekly average abdominal pain score compared to baseline.
- T3MPO-2: 620 subjects were evaluated for 26 weeks of treatment. Responders active vs. placebo: 37% vs. 24% (CI 6-20%). Difference from placebo 13%.
- T3MPO-1: 606 subjects were evaluated for 12 weeks and then were re-randomized to active drug or placebo for a 4-week withdrawal period. Responders active vs. placebo: 27% vs. 19% (CI: 2-15%). Difference from placebo 8%.

VI. The quality of the evidence is considered low given the invalidated subjective endpoints used to determine efficacy and the short duration of therapy evaluated for safety and efficacy.

VII. First-line treatment options for the treatment of IBS-C include dietary modifications, increased fiber intake, and physical activity. Adjunctive pharmacotherapy includes over-the-counter osmotic laxatives. When lifestyle modifications and osmotic laxatives fail to produce sufficient relief of constipation, further pharmacological interventions are indicated. The 2021 American College of Gastroenterology (ACG) clinical guidelines for management of IBS-C recommend use of guanylate cyclase activators (e.g., linaclotide [Linzess], plecanatide [Trulance]) and chloride channel activator (e.g., lubiprostone [Amitiza]) as recommended therapeutic options based on high and moderate quality of clinical evidence, respectively. As of March 2022, the ACG guidelines do not include tenapanor (Ibsrela) as a recommended agent for the treatment of IBS-C. Based on the clinical evidence showing limited treatment effect and lack of place in therapy information, usability of tenapanor (Ibsrela) is uncertain at this time. Thus, use of non-pharmacologic agents and other established therapies are warranted prior to payment consideration for tenapanor (Ibsrela).

References:

1. Ibsrela [Prescribing Information]. Ardelyx, Inc. Fremont, CA. 2019.
2. Zelnorm [Prescribing Information]. Sloan Pharma/WorldMeds LLC. Louisville, KY. 2019.
3. Moayyedi P, Mearin F, Azpiroz F, et al. Irritable bowel syndrome diagnosis and management: A simplified algorithm for clinical practice. United European Gastroenterol J. 2017;5(6):773-788.
4. Chey WD, Lembo AJ, Rosenbaum DP. Efficacy of Tenapanor in Treating Patients With Irritable Bowel Syndrome With Constipation: A 12-Week, Placebo-Controlled Phase 3 Trial (T3MPO-1). Am J Gastroenterol. 2020 Feb;115(2):281-293.
5. Chey WD, Lembo AJ, Yang Y, Rosenbaum DP. Efficacy of Tenapanor in Treating Patients With Irritable Bowel Syndrome With Constipation: A 26-Week, Placebo-Controlled Phase 3 Trial (T3MPO-2). Am J Gastroenterol. 2021 Jun 1;116(6):1294-1303.
6. Weinberg D.S., Smalley W. Heidelbaugh J.J., et al. American Gastroenterological Association institute guidelines on the pharmacological management of irritable bowel syndrome. Gastroenterology. 2014;144: 1146-1148.
7. Lacy BE, Pimentel M, Brenner DM, Chey WD, Keefer LA, Long MD, Moshiree B. ACG Clinical Guideline: Management of Irritable Bowel Syndrome. Am J Gastroenterol. 2021 Jan 1;116(1):17-44.

Hyperphosphatemia in Chronic Kidney Disease (CKD)

Initial Evaluation

I. **Tenapanor (Xphozah)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. The medication is prescribed by, or in consultation with, a nephrologist; **AND**
   C. A diagnosis of **hyperphosphatemia in Chronic Kidney Disease (CKD); AND**
      1. Member is currently receiving and has been stable on maintenance hemodialysis or peritoneal dialysis for 3 months; **AND**
      2. Presence of hyperphosphatemia, defined as serum phosphate levels >5.5mg/dL within the past 3 months; **AND**
      3. Provider attestation that hyperphosphatemia is not due to a reversible/untreated secondary cause (e.g., hypoparathyroidism, high phosphate containing medications/formulations); **AND**
   D. The member has had an inadequate response, contraindication, or intolerance to, all of the following:
      1. Dietary and lifestyle modifications (e.g., low phosphorus diet); **AND**
      2. Three of the following phosphate binders:
         i. Sevelamer hydrochloride or sevelamer carbonate*
         ii. Lanthanum carbonate*
         iii. Sucroferric oxyhydroxide (Velphoro)*
         iv. Ferric Citrate (Auryxia)*

II. Tenapanor (Xphozah) is considered investigational when used for all other conditions, including but not limited to:
   A. Non-dialysis dependent hyperphosphatemia in chronic kidney disease
   B. Irritable bowel syndrome with diarrhea
   C. Mixed irritable bowel syndrome
   D. Chronic idiopathic constipation
   E. Opioid-induced constipation

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has a diagnosis of hyperphosphatemia in chronic kidney disease (CKD); **AND**
IV. Member is currently receiving and has been stable on maintenance hemodialysis or peritoneal dialysis for 3 months; **AND**

V. Member has exhibited improvement or stability of disease symptoms (e.g., reduction of serum phosphate from baseline or maintenance of serum phosphorus levels within normal range <5.5mg/dL)

Supporting Evidence

I. Excess serum phosphate levels promote vascular calcification and induces endothelial dysfunction leading to cardiovascular toxicity and disease. If left untreated, hyperphosphatemia is correlated with vascular and tissue calcifications, bone pain/fractures, and worsening secondary hyperparathyroidism.

II. The diagnosis and management of chronic kidney disease (CKD) in patients on dialysis requires detailed clinical examination, frequent monitoring of labs, and highly individualized treatment regimens. Given the complexities of treatment of hyperphosphatemia in this patient population, supervision or consultation with a nephrologist is required.

III. CKD is defined as abnormalities of kidney structure or function present for greater than 3 months. Estimated Glomerular filtration rate (eGFR) category (G1-G5) is used to categorize CKD. An eGFR ≥90 mL/min/1.73m^2 (G1) is normal or high, eGFR between 60-89 mL/min/1.73m^2 (G2) is considered mildly decreased, 45-59 mL/min/1.73m^2 (G3a) is mildly to moderately decreased, 30-44 mL/min/1.73m^2 (G3b) is moderately to severely decreased, 15-29 mL/min/1.73m^2 (G4) is severely decreased, and <15 ml/min/1.73m^2 (G5) or requiring dialysis is considered kidney failure. Within clinical guidelines, recommendations for treatment of hyperphosphatemia applies to patients in categories G3a-G5d (i.e., GFR <60 mL/min).

IV. Tenapanor (Xphozah) was studied in patients with CKD requiring dialysis, therefore, the safety, efficacy, and utility of tenapanor (Xphozah) in patients without CKD or in those not requiring dialysis has not been established. Patients with CKD requiring dialysis are at greater risk of developing hyperphosphatemia and at higher risk of CKD related morbidity and mortality. Within all Phase III clinical trials, patients were required to be on chronic maintenance hemodialysis for at least 3 months prior to study enrollment.

V. The safety and efficacy of tenapanor (Xphozah) was evaluated in three Phase III trials (AMPLIFY, PHREEDOM, ESRD-HD), and one Phase IV open-label extension trial (NORMALIZE).

- AMPLIFY was a Phase III, double-blind, multicenter, placebo-controlled trial enrolling 236 patients undergoing maintenance dialysis with hyperphosphatemia despite receiving phosphate binder therapy (including sevelamer, non-sevelamer, sevelamer plus non-sevelamer, or multiple non-sevelamer binders). Patients were randomized to receive oral tenapanor (Xphozah) 30 mg twice daily plus phosphate binder or placebo plus phosphate binder for 4 weeks. The primary efficacy endpoint was change in serum phosphorus concentration from baseline to week 4, and key secondary endpoints were proportion of patients with serum phosphorus levels < 5.5mg/dL at weeks 1-4. At week 4, patients receiving tenapanor (Xphozah) plus phosphate binder had a significantly larger least squares mean change in serum phosphorus concentration from baseline when compared to placebo plus phosphate binder (-0.84 vs -0.19 mg/dL, p<0.001). At week 1, 49.1% of patients in the tenapanor (Xphozah) + binder arm achieved serum phosphorus <5.5 mg/dL versus 21.0% of patients for the placebo + binder arm (p<0.001). This effect was sustained through week 2 (41.4% vs 23.5%, p=0.003), week 3 (47.3% vs 17.6%, p <0.001), and week 4 (37.1% vs 21.8%, p=0.01), respectively.
- PHREEDOM was a 564 patient, 52-week, Phase III, multicenter trial consisting of three parts, a 26-week open-label randomized treatment period (RTP), a 12-week

double-blind placebo-controlled randomized withdrawal period (RWP), and a 14-week open-label safety extension period (SEP). After a washout period, patients were randomized 3:1 to either tenapanor (Xphozah) for 26 weeks or sevelamer for 52 weeks. Patients in the tenapanor (Xphozah) arm were randomized into a withdrawal period to be continued on tenapanor (Xphozah) or placebo for 12 weeks, followed by an optional 14-week safety extension period. The primary end point was the change in serum phosphorous from the end of the RTP to the end of the RWP, among participants who achieved ≥1.2 mg/dl decrease in serum phosphate during the RTP (efficacy analysis set). In the ITT population, there was a mean difference of 1.4 mg/dL between baseline phosphate and phosphate at 26 weeks for the tenapanor (Xphozah) arm during the 26-week RTP, and a -0.66 mg/dL difference between tenapanor (Xphozah) and placebo in the 12-week RWP (p=0.002). During the RTP, 53% of patients who received tenapanor (Xphozah) experienced diarrhea as an adverse event vs 7% for sevelamer. Twenty four percent of patients discontinued tenapanor versus 1% in the sevelamer arm during the RTP. Adverse events during the 12-week RWP were similar between placebo and tenapanor. Rates of diarrhea were significantly lower during the 14-week safety extension trial for tenapanor, at 7%.

- ESRD-HD was a 219-patient, Phase III randomized, double-blind trial with two periods following a washout of phosphate binders. Patients were randomized 1:1:1 to tenapanor (Xphozah) 3 mg twice daily, tenapanor 10mg twice daily, or tenapanor 30mg twice daily during the 8-week randomized treatment period (RTP), followed by re-randomization to either placebo or their previous dose of tenapanor (Xphozah) during the 4-week randomized withdrawal period. The primary end point was mean change in serum phosphate over the 4-week withdrawal period for the tenapanor (Xphozah) group (using pooled data) versus the placebo group. In the ITT analysis set, there was a statically significant difference in the primary endpoint between the pool tenapanor group and placebo, mean difference of -0.72 mg/dl (0.07 vs 0.79, p=0.003 for tenapanor (Xphozah) and placebo, respectively). Any adverse events were slightly higher in the 30 mg tenapanor (Xphozah) group when compared to placebo in the RWP, 35.3% vs 25.6%, but serious adverse events were higher in the placebo arm, 4.9% vs 0% for all pooled tenapanor (Xphozah).
- NORMALIZE was an open-label 18-month extension study. Patients entering the study from the tenapanor (Xphozah) arm with serum phosphate levels in the normal range were followed with no medication changes. Patients entering the study from the tenapanor (Xphozah) arm with serum phosphate greater than 4.5 mg/dL had sevelamer tablets added incrementally to achieve normal serum phosphate levels. Patients entering the study from the sevelamer safety control arm had tenapanor (Xphozah) tablets added to their treatment regimen while reducing sevelamer tablets based on their serum phosphate value to achieve normal serum phosphate levels. The primary objective of the study was to evaluate the ability of tenapanor (Xphozah) alone or in combination with sevelamer to achieve serum phosphate levels within the normal range (2.5 to 4.5 mg/dL) in patients with CKD on maintenance dialysis whose serum phosphate levels were greater than 6.0 mg/dL at baseline.
- OPTIMIZE was a 26-week, randomized, open label study, which included 330 patients with CKD on maintenance dialysis with hyperphosphatemia evaluating treatment of hyperphosphatemia in adult patients with CKD on maintenance

dialysis, with tenapanor (Xphozah) alone or in combination with phosphate binders, to achieve target serum phosphate ≤5.5 mg/dL. The study randomized patients on a stable dose of phosphate binder treatment with serum phosphate >5.5mg/dL and ≤10.0 mg/dL in a 1:1 ratio to two different treatment cohorts, as well as patients who were phosphate binder naïve with serum phosphate > 4.5 and ≤10.0 mg/dL in a third cohort.

- Results from NORMALIZE and OPTIMIZE are not yet published at this time.

VI. There are two commonly cited clinical practice guidelines for the management of CKD with threshold and guidance on target ranges for serum phosphate levels. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) 2003 practice guidelines recommend that pharmacological and non-pharmacological approaches be implemented to reduce serum phosphate levels below 5.5mg/dL in patients with CKD Stage 5 requiring dialysis. Within this clinical practice guideline, serum phosphate of >5.5 mg/dL is consistent with hyperphosphatemia. Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of CKD-MBD (2017) recommend to lower elevated serum phosphate levels "toward the normal range" defined as a more stringent 2.5-4.5mg/dL in patients with CKD stages G3a to G5 to. This reference range is cited in part due to the observation that patients with serum phosphate levels close to 4.4 mg/dL had the best survival in observational/epidemiologic studies. The risk of mortality increases in a U-shape pattern from this point, as demonstrated in Block GA et al. (2004) with subsequent observational studies replicating similar findings.

- Block GA et Al. (2004) included 40,538 hemodialysis patients in an observational study which analyzed the relationship between serum phosphorus levels and risk of death. Patients were stratified into serum phosphorous categories of <3 mg/dL, increasing by 1mg/dl groups until > 9mg/dl. The study showed an increasing risk of death and hospitalization with each 1mg/dl increase in serum phosphorus above 5mg/dL. The RR were 1.10 (1.02 to 1.17) and 1.25 (1.18 to 1.33) for serum phosphorus concentrations 5.0 to 5.5 mg/dl and 5.5 to 6.0 mg/dl, respectively, and high serum phosphorus concentrations (≥11.0 mg/dl) were associated with even larger increases in RR (2.47; 95% CI, 1.90 to 3.19).
- A systematic review and meta-analysis by Palmer et al. consisting of 115,552 patients from 16 cohort studies between 1947 and 2010, evaluated the association between levels of serum phosphorus and risks of all-cause and cardiovascular mortality in patients with CKD. Thirteen studies assessed the relationship between serum phosphorus levels and all-cause mortality and 3 studies assessed serum phosphorus levels and CV mortality. The trial noted for every 1 mg/dL increase in serum phosphorus, the risk of mortality increased by 35% (RR 1.35; 95% CI, 1.16-1.57) in adequately adjusted studies, and by 18% (RR 1.18, 95% CI, 1.12-1.25) in the available 13 studies. The risk of CV mortality increased by 10% per 1 mg/dL increase in serum phosphorus (RR, 1.10; 95% CI, 1.06-1.13) in the 3 studies assessing CV mortality.

VII. The quality of evidence is considered low-moderate due to use of study outcomes that have not been directly correlated with improvements in clinically meaningful outcomes such as morbidity, mortality, symptom relief, health-related quality of life, or mental, physical, and emotional functioning. Nevertheless, reduction of phosphate levels in patients with hyperphosphatemia in CKD is an established goal of treatment and is accepted by the FDA as a validated surrogate endpoint based on observational studies that link high phosphate levels to

increased risk of death due to cardiovascular causes. It is not known whether tenapanor (Xphozah) improves morbidity or mortality at this time, however, as demonstrated in the AMPLIFY trial, it lowers phosphate to normal levels (sP<5.5mg/dL) in 37.1% of patients at week 4 and provides consistent reduction in phosphate levels compared to placebo as demonstrated in PHREEDOM and ESRD-HD clinical trials.

VIII. In addition to pharmacotherapy, clinical guidelines recommend limiting dietary phosphorus intake in the treatment of hyperphosphatemia, and it is reasonable to consider phosphorus sources (e.g., animal, vegetable, additives).

IX. There are currently no head-to-head trials comparing the efficacy of tenapanor (Xphozah) to available phosphate binders on the market, and indirect comparison is confounded by different patient populations, study designs, and study parameters. Currently available phosphate lowering agents lower serum phosphate levels by roughly 1.5-2.2 mg/dL and remain the standard of care in patients with CKD undergoing dialysis treatment who require serum phosphate lowering. There are four major classes of agents that have been approved in the US to control serum phosphate levels in adults with CKD on dialysis, including calcium-based binders, sevelamer-based products, lanthanum carbonate, and iron-based binders. Although available phosphate binders have similar phosphorus lowering potential, treatment effect and tolerability can vary in the real-world setting. Due to established safety and efficacy of these agents as well as cost-effectiveness, trial of three phosphate binders is required prior to treatment with tenapanor (Xphozah), unless previously not tolerated, ineffective, or contraindicated. Calcium-based binders are generally not recommended as a first line treatment option due to higher risk of mortality compared to non-calcium-based binders and risks associated with calcium accumulation. Sevelamer and lanthanum carry a contraindication in bowel obstruction and should be used with caution in patients with gastrointestinal (G) disease or with major GI surgery. Sucroferric oxyhydroxide (Velphoro) and ferric citrate (Auryxia) are iron-based binders. There are no contraindications to treatment with sucroferric oxyhydroxide (Velphoro); however, ferric citrate (Auryxia) is contraindicated in iron overload syndromes. Sucroferric oxyhydroxide (Velphoro) is not systemically absorbed, therefore, iron-absorption is minimal. Ferric citrate (Auryxia) may increase serum iron, ferritin, and transferrin saturation (TSAT), which may lead to excessive elevations in iron stores. Serum iron, ferritin, and transferrin saturation (TSAT) should be monitored.

X. Initial authorization is limited to 3 months of therapy as treatment response (e.g., sP lowering) is expected to occur as early as week 1 as shown from the data in AMPLIFY trials. Delayed treatment response beyond 3 months was not shown within the clinical program given the short trial duration of ESRD-HD (12 weeks) and AMPLIFY (4 weeks).

Investigational or Not Medically Necessary Uses

I. Safety and efficacy have not yet been sufficiently established and/or clinical trials are currently underway for the following indications:
   A. Non-dialysis dependent hyperphosphatemia in chronic kidney disease
   B. Irritable bowel syndrome with diarrhea
   C. Mixed irritable bowel syndrome
   D. Chronic idiopathic constipation
   E. Opioid-induced constipation

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) [published correction appears in Kidney Int Suppl (2011). 2017 Dec;7(3):e1]. *Kidney Int Suppl (2011)*. 2017;7(1):1-59. doi:10.1016/j.kisu.2017.04.001
2. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*. 2003;42(4 Suppl 3):S1-S201.
3. Palmer SC, Hayen A, Macaskill P, et al. Serum Levels of Phosphorus, Parathyroid Hormone, and Calcium and Risks of Death and Cardiovascular Disease in Individuals With Chronic Kidney Disease: A Systematic Review and Meta-analysis. *JAMA.* 2011;305(11):1119–1127. doi:10.1001/jama.2011.308
4. Pergola PE, Rosenbaum DP, Yang Y, Chertow GM. A Randomized Trial of Tenapanor and Phosphate Binders as a Dual-Mechanism Treatment for Hyperphosphatemia in Patients on Maintenance Dialysis (AMPLIFY). *J Am Soc Nephrol*. 2021;32(6):1465-1473. doi:10.1681/ASN.2020101398
5. Block GA, Bleyer AJ, Silva AL, et al. Safety and Efficacy of Tenapanor for Long-term Serum Phosphate Control in Maintenance Dialysis: A 52-Week Randomized Phase 3 Trial (PHREEDOM). *Kidney360*. 2021;2(10):1600-1610. Published 2021 Aug 27. doi:10.34067/KID.0002002021
6. Block GA, Rosenbaum DP, Yan A, Chertow GM. Efficacy and Safety of Tenapanor in Patients with Hyperphosphatemia Receiving Maintenance Hemodialysis: A Randomized Phase 3 Trial. *J Am Soc Nephrol*. 2019;30(4):641-652. doi:10.1681/ASN.2018080832
7. Askar AM. Hyperphosphatemia. The hidden killer in chronic kidney disease. *Saudi Med J*. 2015;36(1):13-19. doi:10.15537/smj.2015.1.9843
8. Doshi SM, Wish JB. Past, Present, and Future of Phosphate Management. *Kidney Int Rep*. 2022;7(4):688-698. Published 2022 Feb 1. doi:10.1016/j.ekir.2022.01.1055
9. Bilezikian JP, Brandi ML, Cusano NE, et al. Management of Hypoparathyroidism: Present and Future. *J Clin Endocrinol Metab*. 2016;101(6):2313-2324. doi:10.1210/jc.2015-3910Fishbane SN, Nigwekar S. Phosphate Absorption and Hyperphosphatemia Management in Kidney Disease: A Physiology-Based Review. *Kidney Med*. 2021;3(6):1057-1064. Published 2021 Aug 27. doi:10.1016/j.xkme.2021.07.003
10. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol*. 2004;15(8):2208-2218. doi:10.1097/01.ASN.0000133041.27682.A2
11. Fernández-Martín JL, Carrero JJ, Benedik M, et al. COSMOS: the dialysis scenario of CKD-MBD in Europe. *Nephrol Dial Transplant*. 2013;28(7):1922-1935. doi:10.1093/ndt/gfs418

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
Tegaserod (Zelnorm) Policy	Irritable bowel syndrome with constipation (IBS-C)
Opioid-Induced Constipation Agents Policy	Opioid-induced constipation

Policy Implementation/Update:

Action and Summary of Changes	Date
Changed step therapy requirement for tenapanor (Xphozah) to require trial of three phosphate binders. Added tenapanor (Xphozah), indication for hyperphosphatemia in patients with CKD, and supporting evidence. Remove CKD and hyperphosphatemia from E/I section. Updated alternative requirements for IBS indication to include generic lubiprostone.	12/2023
Policy updated to include pre-requisites of trial of current formulary and preferred agents; removed criteria requiring documentation of pain scores and stool frequency; updated supporting evidence	03/2022
Policy created	02/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP221

Split Fill Management*

Description

Tepotinib (Tepmetko) is an orally administered tyrosine kinase inhibitor (TKI) that targets mesenchymal-epithelial transition (MET).

Length of Authorization

- N/A

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
tepotinib (Tepmetko)	225 mg tablets	Metastatic Non-Small Cell Lung Cancer with a mutation that leads to MET exon 14 skipping	60 tablets/30-day supply

Initial Evaluation

I. **Tepotinib (Tepmetko)** is considered investigational when used for all conditions, including but not limited to Non-Small Cell Lung Cancer.

Renewal Evaluation

I. N/A

Supporting Evidence

I. Tepotinib (Tepmetko) is a tyrosine kinase inhibitor that targets mesenchymal-epithelial transition (MET) and is currently being evaluated in Non-Small Cell Lung Cancer (NSCLC) that contains a mutation that leads to MET exon 14 skipping. The clinical trial dose is 500 mg orally once daily.

II. Tepotinib (Tepmetko) is the second therapy FDA-approved for this specific NSCLC mutation, joining capmatinib (Tabrecta). Other therapies that have been utilized in this setting include crizotinib (Xalkori), platinum-based doublet chemotherapy with or without bevacizumab, and/or immunotherapy (e.g., pembrolizumab); however, available data to support efficacy in this population is limited, and response to therapy is generally poor.

III. Place in therapy is likely to be in the advanced or metastatic setting based on the population being evaluated in the clinical trial, and may be utilized as first-line in these stages; however, given the limited safety and efficacy data to support its use, other therapies may be considered prior to tepotinib (Tepmetko). As of October 2020, the NCCN treatment guidelines had not yet included tepotinib (Tepmetko). Tepotinib (Tepmetko) is mentioned in the ESMO treatment guideline as a treatment option for this population, alongside capmatinib (Tabrecta) and investigational agent savolitinib.

IV. The pivotal trial for tepotinib (Tepmetko) is the VISION trial, which is an open-label, Phase 2, multi-cohort, single-arm, ongoing trial. Patients with MET exon 14 skipping mutations or MET-amplified disease across various treatment settings (e.g., treatment naïve vs. pretreated) were included in the trial. Patients were negative for EGFR mutations or ALK rearrangements, and those with brain metastases were allowed. Ninety-nine patients are being evaluated for efficacy, and the safety profile is based on 152 patients. The average patient age was 74 years, 97% had metastatic disease, 43% were treatment native in the advanced/metastatic setting, 33% received one prior therapy, and 11% had two or more prior therapies. Japanese patients were excluded, due to an ongoing trial specific to that population.

V. Objective response was seen in 46 patients (46%), all of which were partial responses. Duration of response was 11.1 months, progression-free survival was 8.5 months, overall survival 17.1 months, and EORTC-QLQ-LC13 cough symptom quality of life scores showed a 13-15 point reduction.

VI. Tepotinib (Tepmetko) was granted Breakthrough Therapy designation, Priority Review, and is being evaluated under FDA Real-Time Oncology Review (RTOR) pilot program – intended to be a more efficient review process to bring safe and effective treatment to patients as early as possible. The application is supported by the results of the Phase 2, ongoing VISION study that has shown potential anti-tumor activity via response rate.

VII. True medication safety and efficacy of tepotinib (Tepmetko) remain unknown given the observational nature of the trial (i.e., lack of comparator arm and open-label study design).

VIII. Safety of tepotinib (Tepmetko) has been evaluated in 152 patients, with a median exposure of 6.9 months. Eighty-nine percent of patients experienced treatment related adverse events (AE). Common AE were peripheral edema (63%), nausea (26%), diarrhea (26%), creatinine increase (18%), hypoalbuminemia (16%), amylase increase (11%), lipase increase (9%), asthenia (8%), anorexia (8%), pleural effusion (8%), and alopecia (8%).

IX. Grade 3 or 4 AE occurred in 28% of patients, mainly peripheral edema and amylase and lipase increases. Serious AE's occurred in 15%, 11% permanently discontinued due to AE's overall, and 33% of patents had a dose reduction due to AE's. Peripheral edema was the most common reason for discontinuation or dose reduction. Sixteen percent of patients had dose reduction and 18% had dose interruption based on this AE alone. Twenty-one patients had an AE leading to death while on tepotinib (Tepmetko), one of which was due to interstitial lung disease determined as related to tepotinib (Tepmetko) therapy. Currently there is unknown clinical benefit/value of tepotinib (Tepmetko), and the safety risks are outweighing until further evidence is available to support safety and efficacy of tepotinib (Tepmetko). Of note, tepotinib (Tepmetko) is in several ongoing clinical trials alone and in combination with other chemotherapeutic agents for NSCLC.

X. Insight from oncology specialists indicate that the diagnosis of stage IV metastatic disease can include intra-pulmonary (disease contained within the lungs) and extra-pulmonary (disease spread to organs outside the lungs) metastases. Intra-pulmonary metastases are typically staged as M1a and described as one of the following situations: separate nodule in the other lung, pleural or pericardial nodules, or malignant pleural or pericardial effusions. The treatment approach for those with intra-pulmonary metastases should be individualized and include surgery and, when surgery is not feasible, standard systemic therapy.

Investigational or Not Medically Necessary Uses

I. Tepotinib (Tepmetko) has not been sufficiently studied for safety and efficacy for any condition to date.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Paik P.K., Felip E., Veillon R., et al. Tepotinib in non-small-cell lung cancer with MET exon 14 skipping mutations. N Engl J Med. 2020; 383(10): 931-943.
2. Tepmetko [Prescribing Information]. Merck KGaA. Darmstadt, Germany. February 2021.
3. Tabrecta [Prescribing Information]. Novartis Pharmaceuticals Corporation. East Hanover, NJ. May 2020.
4. Kong-Beltran M, Seshagiri S, Zha J, et al. Somatic mutations lead to an oncogenic deletion of MET in lung cancer. Cancer Res. 2006;66(1):283-289.
5. National comprehensive Cancer Network. NCCN Guidelines: Non-small Cell Lung Cancer V8.2020. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated September 15, 2020.
6. European Society for Medical Oncology. Metastatic non-small-cell lung cancer. ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. September 15, 2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added supporting evidence around stage IV metastatic disease and metastases.	10/2021
Policy created	02/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP157

Description

Tetrabenazine (Xenazine), deutetrabenazine (Austedo) and valbenazine (Ingrezza) are reversible vesicular monoamine transporter 2 (VMAT2) inhibitors that act by regulating monoamine uptake from the cytoplasm to the synaptic vesicle. Its mechanism of action in Tardive dyskinesia or chorea-reduction is unknown.

Length of Authorization

- Initial:
  - i. Tardive dyskinesia: Six months
  - ii. Chorea associated with Huntington's disease: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
tetrabenazine (Xenazine)	12.5 mg	Chorea associated with Huntington's disease	60 tablets/30 days
	25 mg		
	25 mg	Chorea associated with Huntington's disease, genotyped *extensive* and *intermediate metabolizers*	120 tablets/30 days
generic tetrabenazine	12.5 mg	Chorea associated with Huntington's disease	60 tablets/30 days
	25 mg		
	25 mg	Chorea associated with Huntington's disease, genotyped *extensive* and *intermediate metabolizers*	120 tablets/30 days
deutetrabenazine (Austedo)	6 mg	Tardive dyskinesia in adults; Chorea associated with Huntington's disease	210 tablets/30 days
	9 mg		60 tablets/30 days
	12 mg		120 tablets/30 days
deutetrabenazine (Austedo XR)	6mg, 12mg, 24mg titration tab kit	Tardive dyskinesia in adults; Chorea associated with Huntington's disease	42 tablets/28 days
	6 mg		210 tablets/30 days
	12 mg		90 tablets/30 days
	24 mg		60 tablets/30 days
valbenazine (Ingrezza)	40 mg	Tardive dyskinesia; Chorea associated with Huntington's disease	30 capsules/30 days; 4-week Initiation Pack
	80 mg		

Initial Evaluation

I. **Tetrabenazine (Xenazine), deutetrabenazine (Austedo) and valbenazine (Ingrezza)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a neurologist or psychiatrist; **AND**
   C. Medication will not be used in combination with another VMAT2 inhibitor [e.g. tetrabenazine (Xenazine), deutetrabenazine (Austedo) valbenazine (Ingrezza)], monoamine oxidase inhibitor (MAOI) [e.g. isocarboxazid (Marplan®), phenelzine, tranylcypromine, reserpine]; **AND**
   D. Provider attestation that member does not have uncontrolled symptoms of depression, agitation, psychosis, or increased risk of suicidality; **OR**
      1. Provider attestation that the potential benefit of treatment with VMAT2-I outweighs the risk of depression or suicidality; **AND**
   E. A diagnosis of one of the following:
      1. **Chorea associated with Huntington's disease**; **AND**
         i. For BRAND tetrabenazine (Xenazine) or generic tetrabenazine:
            a. Provider attestation that doses exceeding 50mg per day are to be reserved for extensive and intermediate metabolizers (see quantity limit table based on metabolizer status); **AND**
               i. If request is for BRAND tetrabenazine (Xenazine), treatment with generic tetrabenazine, deutetrabenazine (Austedo), and valbenazine (Ingrezza) has been ineffective, contraindicated or not tolerated; **OR**
      2. **Tardive dyskinesia**; **AND**
         i. The request is for generic tetrabenazine, valbenazine (Ingrezza) and deutetrabenazine (Austedo); **AND**
         ii. Member has failed to respond to a change or is unable to switch current antidopaminergic therapy

II. Tetrabenazine (Xenazine), deutetrabenazine (Austedo), and Valbenazine (Ingrezza) are considered investigational when used for all other conditions, including but not limited to:
   A. Tourette's syndrome

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms.

Supporting Evidence

I. Safety and effectiveness of VMAT2 inhibitors have not been established in pediatric patients.

II. Agents in this policy are required to be prescribed by or in consultation with a neurologist or psychiatrist considering the seriousness of adverse effects (depression and suicidality, cognitive decline, Parkinsonism, dysphagia, sedation/somnolence, akathisia, restlessness, and disability), complexity of the disease state, and dosing of the medication.

III. Concomitant use of tetrabenazine (Xenazine), deutetrabenazine (Austedo), and valbenazine (Ingrezza) with MAOIs may increase the concentration of monoamine neurotransmitters in synapses, potentially leading to increased risk of adverse reactions such as serotonin syndrome, or attenuated treatment effect. Tetrabenazine (Xenazine), deutetrabenazine (Austedo), and valbenazine (Ingrezza) should not be used in combination with an MAOI.

IV. The International Guidelines for the Treatment of Huntington's Disease recommend tetrabenazine (VMAT2-I) as first line for chorea management except for patients who have, "not well-managed depression or suicidal thoughts" due to the side effects of the drug class. In patients with psychiatric disorders or personality/behavioral disorders that increase suicide risk, the guidelines recommend the use of 2nd generation neuroleptics. Treatment with a single agent is preferred due to the risk of additional adverse effects. Additionally, compendia cites comorbid depression, agitation, and/or psychosis as criteria for determining whether a VMAT2-I is appropriate based on patient comorbidities.

V. Per the Physician's Guide to the Management of Huntington's Disease 3rd edition, providers often treat chorea with neuroleptics (e.g., aripiprazole, haloperidol, fluphenazine, risperidone, olanzapine) based on clinical experience and due to safety concerns associated with VMAT2-inhibitors, namely: decreased cognition and mood, increased suicidality and depression. Studies of the anti-choreic effects of neuroleptics were excluded from the AAN guideline review due to criteria set forth; however, the AAN acknowledges neuroleptics are commonly used in clinical practice to treat chorea and recommends additional study in recognition of this use. In consideration of the Boxed Warnings and adverse effects associated with this class, a trial of therapy often considered in standards-of-care is reasonable.

VI. KINECT-HD was a phase 3, randomized, double-blind, placebo-controlled trial which studied valbenazine (Ingrezza) vs placebo for 12 weeks. The trial included 125 participants (valbenazine n=64, placebo n=61) with a moderate level of disease advancement per UHDRS TFC (Total Functional Capacity) scores for Huntington's chorea. The primary endpoint of the study was assessing the mean change in UHDRS-TMC (Unified Huntington's Disease Rating Scale –Total Maximal Chorea) from baseline to the end of the study at week 12. The results demonstrated a statistically and clinically significant improvement in the primary endpoint for valbenazine vs placebo (-4.6 vs 1.4, difference -3.2, 95% CI –4.4 to –2.0, $p<0.0001$). The secondary endpoints included Clinical Global Impression of Change (CGI-C) and Patient Global Impression of Change (PCI-C) at week 12, and mean changes from baseline to week 12 in short-form Quality of Life in Neurological (NeuroQoL) Disorders Upper Extremity and Lower Extremity Function T-scores. By week 12, there was a statistically significant difference in the CGI-C and PGI-C scores compared to baseline (p=-.0007, p=0.0062). However, the new secondary measures within the study (NeuroQoL) indicated no statistically significant change when compared to placebo (p=0.3304). In terms of safety, the results listed no worsening of anxiety, depression, akathisia, parkinsonism, or new reports of suicidal ideation.

VII. No sufficient evidence was found to show superiority of one agent over the other.

VIII. When clinically appropriate, the two main strategies of pharmacotherapy in patients who are showing signs of tardive dyskinesia include discontinuation of the offending drug and switching from a first- to a second-generation antipsychotic drug because second generation neuroleptics have a lower risk of TD.

IX. Additional pharmacologic options [e.g. benzodiazepines, anticholinergic drugs (trihexyphenidyl, benztropine)] have been used in clinical practice for many years. AAN states use of benzodiazepines and tetrabenazine (Xenazine) as standard of care treatments is based on weak clinical evidence but it has been standard of care. According to the 2012 AAN guidelines, amantadine or riluzole could be other agents prescribed for chorea management (Level B).

X. There is a lack of head-to-head trials and scientific evidence to show superiority of one medication over the other. There is history of use with tetrabenazine in tardive dyskinesia.

XI. For patients with a diagnosis of TD, additional pharmacologic interventions include the use of benzodiazepines, botulinum toxin injections, or tetrabenazine (Xenazine) to control symptoms of TD, paradoxically, resuming treatment with antipsychotic drugs in order to suppress TD.

Investigational or Not Medically Necessary Uses

I. Tourette's syndrome
   A. Tetrabenazine (Xenazine)
      A. VMAT2 inhibitors currently available in the United States include deutetrabenazine and valbenazine. Although both are being investigated in the treatment of TS, they, like tetrabenazine (Xenazine), are not yet approved by the US Food and Drug Administration (FDA).
      B. There is insufficient evidence to support the use of tetrabenazine (generic, Xenazine) for the treatment of other movement disorders, including, but not limited to dystonic tremor, or Tourette's syndrome.
   B. Deutetrabenazine (Austedo)
      i. Deutetrabenazine (Austedo) is currently being investigated for use in Tourette's syndrome in:
         a. A Pilot Study Of SD-809 (Deutetrabenazine) In Moderate To Severe Tourette Syndrome
         b. A Randomized, Double-blind, Placebo-controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Tourette Syndrome in Children and Adolescents
      ii. Although deutetrabenazine (Austedo) is being studied for the treatment of Tourette's syndrome, there is currently no published evidence supporting its safety or efficacy in this setting.
   C. Valbenazine (Ingrezza)
      1. Valbenazine (Ingrezza) is currently being investigated for use in Tourette's syndrome; however, initial studies have not demonstrated efficacy for this condition.
         i. In a phase 2 trial in pediatric patients with tics associated with Tourette's syndrome, valbenazine (Ingrezza) did not meet the pre-specified primary endpoint of change from baseline between the placebo valbenazine

(Ingrezza) in the Yale Global Tic Severity Scale (YGTSS) at week six in the intent-to-treat population.

ii. Based on the above results, a second phase 2 trial will aim to evaluate a higher dose of valbenazine (Ingrezza) to suppress tics in pediatric patients.

2. Although valbenazine (Ingrezza) is being studied for the treatment of Tourette's syndrome, there is currently no published evidence supporting its safety or efficacy in this setting.

References

1. Austedo [Prescribing Information]. Teva Pharmaceuticals USA, Inc.: North Wales, PA. May 2022
2. Xenazine [Prescribing Information]. Lundbeck Inc.: Deerfield, IL. June 2015
3. Ingrezza [Prescribing Information]. Neurocrine Pharmaceuticals; San Diego, CA. August 2023
4. Rosenblatt A, Ranen NG, Nance MA, Paulsen JS. A physician's guide to the management of Huntington's disease, 3rd Ed, Huntington 's disease Society of America, New York 2011.
5. 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
6. Ondo WG, Hanna PA, Jankovic J. Tetrabenazine treatment for tardive dyskinesia: assessment by randomized videotape protocol. Am J Psychiatry. 1999;156(8):1279-1281.[PubMed 10450276]
7. Roongroj Bhidayasiri, Onanong Jitkritsadakul, Joseph H. Friedman, Stanley Fahn. Updating the recommendations for treatment of tardive syndromes: A systematic review of new evidence and practical treatment algorithm. Journal of the Neurological Sciences. (Jun 2018) 389, 67-75. https://doi.org/10.1016/j.jns.2018.02.010 https://www-sciencedirect-com.liboff.ohsu.edu/science/article/pii/S0022510X18300686
8. Godwin-Austen RB, Clark T. Persistent phenothiazine dyskinesia treated with tetrabenazine. Br Med J. 1971;4(5778):25-26.[PubMed 4938245]
9. UpToDate, Inc. Huntington disease: Management. UpToDate [database online]. Updated August 25, 2023 Accessed August 31,2023
10. Rukovets, O. (2013). TREATING AND MANAGING TARDIVE SYNDROMES. The American Academy of Neurology (AAN), 13(17), 1–3. doi: 10.1097/01.nt.0000434605.49176.25
11. Efficacy, Safety, and Tolerability of Valbenazine for the Treatment of Chorea Associated With Huntington's Disease (KINECT-HD), ClinicalTrials.gov Identifier: NCT04102579, https://clinicaltrials.gov/ct2/show/NCT04102579?term=valbenazine&draw=2&rank=4
12. A Pilot Study Of SD-809 (Deutetrabenazine) In Moderate To Severe Tourette Syndrome, ClinicalTrials.gov Identifier: NCT02674321, https://clinicaltrials.gov/ct2/show/NCT02674321?term=deutetrabenazine&draw=2&rank=4
13. A Randomized, Double-blind, Placebo-controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Tourette Syndrome in Children and Adolescents, ClinicalTrials.gov Identifier: NCT03452943, https://clinicaltrials.gov/ct2/show/NCT03452943?term=deutetrabenazine&draw=2&rank=7
14. Safety and Efficacy of NBI-98854 (valbenazine) in Pediatric Subjects With Tourette Syndrome, ClinicalTrials.gov Identifier: NCT03530293, https://clinicaltrials.gov/ct2/show/NCT03530293?term=valbenazine&draw=2&rank=7
15. Bachoud-Lévi AC, Ferreira J, Massart R, et al. International Guidelines for the Treatment of Huntington's Disease. *Front Neurol*. 2019;10:710. Published 2019 Jul 3. doi:10.3389/fneur.2019.00710
16. Reilmann R. Pharmacological treatment of chorea in Huntington's disease-good clinical practice versus evidence-based guideline. *Mov Disord*. 2013;28(8):1030-1033. doi:10.1002/mds.25500

Policy Implementation/Update:

Action and Summary of Changes	Date
Added Huntington's chorea indication for valbenazine (Ingrezza). Removed the step through generic tetrabenazine. Updated initial authorization for Tardive Dyskinesia indication to 6 months following standard authorization.	12/2023
Adding Austedo XR titration tablet kit	07/2023
Added Austedo XR to QL table	04/2023

Updated QL for 6mg and 9mg Austedo tablets; updated formatting	01/2023
• Updated criteria to policy format and combined separate polices into one • Generic tetrabenazine added to tardive dyskinesia criteria • For deutetrabenazine (Austedo) only: Treatment with generic tetrabenazine and valbenazine (Ingrezza) has been ineffective, contraindicated or not tolerated • Medication will not be used in combination with another VMAT2 inhibitor , monoamine oxidase inhibitor (MAOI) [e.g. isocarboxazid (Marplan®), phenelzine, tranylcypromine, reserpine], it is contraindicated	12/2019
Added Tardive Dyskinesia indication for deutetrabenazine (Austedo™)	09/2017
Updated question 5 for valbenazine (Ingrezza™) based on P&T recommendations	08/2017
Previous Reviews	05/2017; 06/2017; 09/2017; 08/2019; 12/2019;

Policy Type: PA Pharmacy Coverage Policy: UMP279

Description

Tezepelumab (Tezspire) is a thymic stromal lymphopoietin (TSLP) blocker

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
tezepelumab (Tezspire)	Severe Asthma	210 mg/1.91 mL prefilled pen	1 prefilled pen/30 days
Provider Administered Agents*,++			
tezepelumab (Tezspire)	Severe Asthma	210 mg/1.91 mL prefilled syringe*	1 prefilled syringe/30 days

**Medical drug that requires administration by a healthcare professional and is not available for self-administration by the member, considered one of the excluded classes under the prescription benefit. Prefilled syringe is only FDA approved for provider administration.*

++Certain groups have opted into the pharmacy benefit optimization (PBO) program in which case selected infused specialty medications will only be covered under the pharmacy benefit, and claims submitted under the medical benefit will be denied as provider liability. For more details, please reference: https://www.modahealth.com/medical/injectables/

Initial Evaluation

I. **Tezepelumab (Tezspire)** may be considered medically necessary when the following criteria are met:
   A. Member is 12 years of age or older; **AND**
   B. The request is for tezepelumab (Tezspire) prefilled pen; **AND**
   C. Medication is prescribed by, or in consultation with, a physician specializing in allergy, pulmonology, immunology, or ENT (ear, nose, throat); **AND**
   D. The medication will not be used in combination with another monoclonal antibody for the treatment of asthma (e.g., Dupixent [dupilumab], Xolair [omalizumab], Fasenra [benralizumab], Nucala [mepolizumab], Cinqair [reslizumab], etc.); **AND**
   E. A diagnosis of **severe asthma** when the following are met:
      1. Member has **SEVERE** asthma as defined by one of the following:
         i. Symptoms throughout the day
         ii. Nighttime awakenings, often 7x/week
         iii. SABA (e.g., albuterol, levalbuterol) use for symptom control occurs several times per day
         iv. Extremely limited normal activities
         v. Lung function (percent predicted FEV1) <60%
         vi. Exacerbations requiring oral systemic corticosteroids are generally more frequent and intense relative to moderate asthma; **AND**

2. Member must have two or more exacerbations in the previous year requiring daily oral corticosteroids for at least 3 days (in addition to the regular maintenance therapy defined below); **AND**
3. Member is currently being treated with:
    i. A medium- to high-dose, or maximally tolerated inhaled corticosteroid (ICS) [e.g., budesonide, fluticasone, mometasone]; **AND**
        a. One additional asthma controller medication (e.g., long-acting beta-2 agonist [LABA] {e.g., Serevent Diskus}, long-acting muscarinic antagonist [LAMA] {e.g., Spiriva Respimat}; **OR**
    ii. A maximally tolerated dose of ICS/LABA combination product (e.g., Advair, Airduo, Breo, Dulera, Symbicort); **AND**
4. Background controller medications (e.g., Advair, Airduo, Breo, Dulera, Symbicort) will be continued with the use of tezepelumab (Tezspire), unless all are contraindicated; **AND**
5. Member meets <u>one</u> of the following scenarios (i, ii, or iii):
    i. Tezepelumab (Tezspire) will be used to treat severe asthma with an eosinophilic phenotype (i.e., blood eosinophils ≥150 cells/µL within the last 12 months); **AND**
        a. Treatment with dupilumab (Dupixent) AND mepolizumab (Nucala) have been ineffective, contraindicated, or not tolerated; **OR**
    ii. Tezepelumab (Tezspire) will be used to treat severe asthma with an allergic phenotype (i.e., serum total IgE level, measured before the start of treatment, of ≥ 30 IU/mL and ≤ 700 IU/mL); **AND**
        a. Treatment with omalizumab (Xolair) has been ineffective, contraindicated, or not tolerated; **OR**
    iii. Attestation that member does <u>not</u> have severe asthma with an eosinophilic or allergic phenotype.

II. Tezepelumab (Tezspire) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
    A. Non-severe asthma
    B. Chronic obstructive pulmonary disease (COPD)
    C. Prurigo nodularis
    D. Eosinophilic esophagitis
    E. Chronic rhinosinusitis with nasal polyposis (CRSwNP)
    F. Atopic dermatitis

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Must not be used in combination with another monoclonal antibody (e.g., Dupixent [dupilumab], Xolair [omalizumab], Fasenra [benralizumab], Nucala [mepolizumab], Cinqair [reslizumab], etc.); **AND**

IV. Member has exhibited improvement or stability of disease symptoms (e.g., reduced asthma exacerbations, FEV1, reduced systemic corticosteroid requirements, reduced hospitalizations); **AND**

V. Background controller medications (e.g., ICS/LABA product listed above) will be continued with the use of tezepelumab (Tezspire) unless contraindicated.

Supporting Evidence

I. Tezepelumab (Tezspire) is FDA approved as an add-on maintenance treatment for patients 12 years and older with severe asthma. Efficacy and safety in those under 12 years of age has not been evaluated in clinical trials.

II. Tezepelumab (Tezspire) trials excluded concomitant biologic therapy; moreover, there is a lack of evidence supporting treatment with dual use of biologic therapies and a potential for increased risk of side effects.

III. The Global Initiative for Asthma (GINA) 2022 guidelines define severe asthma as asthma that remains uncontrolled despite optimized treatment with high dose ICS-LABA, or that requires high dose ICS-LABA to prevent it from becoming uncontrolled. Severe asthma must be distinguished from asthma that is difficult to treat due to inadequate or inappropriate treatment, or persistent problems with adherence or comorbidities such as chronic rhinosinusitis or obesity as there are very different treatment implications compared with if asthma is relatively refractory to high dose ICS-LABA or even OCS. GINA guidelines recommend the addition of respiratory biologics after inadequate asthma control despite good adherence and inhaler technique on maximized Step 4 therapy (i.e., medium dose ICS-LABA and reliever therapy or medium or high dose ICS-LABA with as needed SABA).

IV. The labeled indication for tezepelumab (Tezspire) is not dependent on the presenting phenotype for severe asthma. However, balancing the safety and efficacy of other respiratory biologics, trial of targeted eosinophilic or allergic asthma agents will be required prior to treatment with tezepelumab (Tezspire).

V. Tezepelumab (Tezspire) was studied in two registrational, multicenter, randomized, double-blind, placebo-controlled trials – PATHWAY and NAVIGATOR. In both studies participants with severe asthma received tezepelumab (Tezspire) 210 mg or placebo subcutaneously once every four weeks for 52 weeks. The primary efficacy outcome in both trials was the annualized rate or asthma exacerbations (AAER). An asthma exacerbation was defined as worsening of asthma requiring the use of or increase in oral or injectable corticosteroids for at least 3 days, or a single depo-injection of corticosteroids, and/or emergency department visits requiring use of oral or injectable corticosteroids and/or hospitalization.

- PATHWAY
    i. PATHWAY (N=550) was a phase 2b, randomized, multicenter, double-blind, placebo-controlled trial. Participants were randomized 1:1:1:1 to receive tezepelumab (Tezspire) 70 mg, 210 mg, 280 mg, or placebo subcutaneously every four weeks. Baseline characteristics between the treatment groups

were similar. Average age 51.6 years, 65.6% female, 92.5% white, average BMI 28, 49% on high dose ICS, ACQ-6 score 2.68, AQLQ 4.14, FEV1, and mean blood eosinophil counts 367 ± 361 for tezepelumab groups. The AAER, was found to be statistically significant for each dose compared to placebo.

ii. The 210 mg group had the highest relative reduction compared to placebo. Secondary endpoints were statistically significant for the 210 mg dose; however, clinical significance was not realized. Reported endpoints were smaller than the minimal clinically important differences for the ACQ-6 and AQLQ(S) +12 scores (0.5-point difference on these scales) as well as the FEV1 (100 to 200mL difference).

PATHWAY	Placebo	Tezepelumab (210 mg)	Reported Differences (95% CI)	p-Value
AAER	0.72 (0.61, 0.86)	0.20 (0.14, 0.28)	71% (54, 82)	<0.001
FEV_1 (ΔL)	-0.06	0.08	0.13 (0.03, 0.23)	0.009
ACQ-6	-0.91	-1.26	-0.36 (-0.58, -0.13)	0.002
AQLQ(S)+12	0.91	1.25	0.33 (0.09, 0.58)	0.008

- NAVIGATOR

i. NAVIGATOR was a phase III, multicenter, randomized, double-blind, placebo-controlled study (N= 1,161). Baseline characteristics between the treatment groups were similar. Average age 49.5 years, 36.5% male, 62.2% white, average BMI 28.5, 75.1% on high dose ICS, ACQ-6 score 2.8, mean blood eosinophil count 340 (58.4% <300 cells/µL), and 68.5% had IgE positive disease.

NAVIGATOR	Tezepelumab 210 mg	Placebo	Reported Differences (95% CI)	p-Value
Overall Population				
FEV1 (Δ L)	0.23	0.09	0.13 (0.08 to 0.18)	<0.001
ACQ-6	-1.55	-1.22	-0.33 (-0.46 to -0.20)	<0.001
AQLQ(S) +12	1.49	1.15	0.34 (0.20 to 0.47)	<0.001
ASD	-0.71	-0.59	-0.12 (-0.19 to -0.04)	0.002
Blood Eosinophils <150 cells/µL				
FEV1 (Δ L)	0.10	0.07	0.03 (-0.07 to 0.13)	-
ACQ-6	-1.17	-1.08	-0.09 (-0.33 to 0.16)	-
AQLQ(S) +12	1.07	0.96	0.11 (-0.16 to 0.37)	-
ASD	-0.53	-0.53	(-0.15 to 0.15)	-

ii. The AAER in the overall population was 0.93 (95% CI; 0.80 to 1.07) in the tezepelumab group and 2.10 (95% CI; 1.84 to 2.39) in the placebo group (RR, 0.44 (95% CI; 0.37 to 0.53; p<0.001). For patients with a blood eosinophil count of < 300 cells/µL the AAER was 1.02 (95% CI, 0.84 to 1.23) in the tezepelumab group and 1.73 (95% CI, 1.46 to 2.05) in the placebo group (RR, 0.59; 95% CI, 0.46 to 0.75; p<0.001).

iii. Secondary endpoints were all found to be statistically significant; however, minimal clinically important differences were not met to warrant clinical significance for the ACQ-6 and AQLQ(S)+12 in the overall population. Secondary endpoints did not reach statistical significance in the <150 cells/µL subgroup.

- The quality of evidence for tezepelumab (Tezspire) is considered moderate. There is data to support statistically significant reductions in AAER and secondary endpoints; however, not all endpoints were found to meet the minimal clinically important differences. Subpopulation analysis in those with blood eosinophils <150 cells/µL

did not reach statistically significant differences compared to placebo for secondary endpoints. Only 80 adolescent trial participants were included in the registrational trials which may reduce generalizability. Non-white populations were not adequately represented. There is uncertainty in how this therapy will perform head-to-head against other biologics.

VI. Tezepelumab (Tezspire) was studied in a phase 3 oral corticosteroid sparing study (SOURCE). That ran parallel with the NAVIGATOR study.
- SOUCE was a multicenter, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and safety of the medication in reducing oral corticosteroid use in adults with oral corticosteroid dependent asthma. The study ran for 48 weeks in 150 adult patients. Participants also had to be treated with ICS and a long-acting beta 2 agonist along with chronic treatment with oral corticosteroids (OCS).
- Study protocol was published but not the study results themselves; however, AstraZeneca released a statement in December of 2020 that the primary endpoint, significant reduction in the daily OCS dose, without loss of asthma control, with tezepelumab compared to placebo was not met (odds ratio [OR] 1.28, 95% CI 0.69 to 2.35). However, safety profile was reported to be consistent with previous trials.

VII. Patients who completed the NAVIGATOR or SOURCE studies had the opportunity to enroll in DESTINATION, a phase 3 long-term extension study aiming to evaluate the safety and efficacy of tezepelumab over a period of up to 2 years (inclusive of the treatment period of either predecessor study).
- The primary objective of DESTINATION is to assess the long-term safety and tolerability of tezepelumab compared with placebo. For individuals who initially received tezepelumab (n=528) in NAVIGATOR, incidence of adverse events over 104 weeks was 49·62 (95% CI 45·16 to 54·39) per 100 patient-years, compared with 62·66 (56·93 to 68·81) for those receiving placebo (n=531; difference −13·04, 95% CI −17·83 to −8·18). For serious adverse events, incidence was 7·85 (6·14 to 9·89) per 100 patient-years for individuals who initially received tezepelumab and 12·45 (9·97 to 15·35) for those who received placebo (difference −4·59, −7·69 to −1·65). Incidence of serious adverse events was 13·14 (7·65 to 21·04) per 100 patient-years for those who initially received tezepelumab and 17·99 (10·66 to 28·44) for those who received placebo (difference −4·85, −14·88 to 4·53). Tezepelumab reduced the annualized asthma exacerbation rate over 104 weeks compared with placebo. In participants initially from NAVIGATOR, the annualized asthma exacerbation rate ratio over 104 weeks was 0·42 (95% CI 0·35 to 0·51).

VIII. Tezepelumab (Tezspire) was approved for self-administration in February 2023 based on results from the PATHFINDER clinical trial program which included PATH-BRIDGE (phase 1) and PATH-HOME (phase 3).
- PATH-HOME was a phase 3, multicenter, randomized, open-label, parallel-group study where 216 patients were randomized to receive tezepelumab (Tezspire) via a pre-filled syringe (N=111) or an autoinjector (N=105). Under the trial protocol the first, second, third and final doses were administered in the clinic (weeks 0, 4 and 8), the fourth and fifth doses were administered at home (weeks 12 and 16), and the

sixth and final dose was administered in clinic (week 20). The primary endpoint was the proportion of successful administrations of tezepelumab (Tezspire).

- Baseline demographics and clinical characteristics in both device groups were representative of the targeted clinical population. Median age was 47.2 (18.2) years – 24 adolescent patients were included, 50% were female, mean duration of asthma was 20.1 (15.5) years, mean ACQ-6 baseline was 2.23 (0.73) in the PFS group and 2.08 (0.62) in the AI group.
- Tezepelumab (Tezspire) was successfully administered via a PFS by 91.7% of the participants (100/109) and via AI by 92.4% (97/105). Overall, 95.4–97.1% of at-home administrations were successful across device groups. Malfunction occurred in 6 of 655 dispensed APFSs and 5 of 624 dispensed AIs. Of the six APFSs reported as malfunctioning three were used in the clinic (two by HCPs and one by a patient) and three were used at home (two by patients and one by a caregiver). In the AI group, all five devices reported as malfunctioning were used in the clinic by patients (no devices were reported as malfunctioning during at-home use). No mechanical or design-related issues were found during in vitro evaluation of the devices that were reported as malfunctioning.

IX. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for an increased dosing frequency.

Investigational or Not Medically Necessary Uses

I. Tezepelumab (Tezspire) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Non-severe asthma
   B. Chronic obstructive pulmonary disease (COPD)
   C. Prurigo nodularis
   D. Eosinophilic esophagitis
   E. Chronic rhinosinusitis with nasal polyposis (CRSwNP)

References

1. Tezspire. Package Insert. AstraZeneca Pharmaceuticals LP; February 2023.
2. Corren J, Parnes JR, Wang L, et al. Tezepelumab in Adults with Uncontrolled Asthma [published correction appears in N Engl J Med. 2019 May 23;380(21):2082]. N Engl J Med. 2017;377(10):936-946. doi:10.1056/NEJMoa1704064
3. Menzies-Gow A, Corren J, Bourdin A, et al. Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma. N Engl J Med. 2021;384(19):1800-1809. doi:10.1056/NEJMoa2034975
4. Rind DM, McQueen RB, Herron-Smith S, Herce-Hagiwara B, Gutierrez E, Campbell J, Fluetsch N, Pearson SD. Tezepelumab for Severe Asthma; Evidence Report. Institute for Clinical and Economic Review, November 4, 2021.
5. Global Initiative for Asthma Global Strategy for Asthma Management and Prevention, 2022. Available from: www.ginasthma.org

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
dupilumab (Dupixent®) Policy	Asthma (moderate to severe)
	Atopic Dermatitis (moderate to severe)
	Chronic rhinosinusitis with nasal polyposis
	Eosinophilic esophagitis
	Prurigo nodularis
omalizumab (Xolair®) Policy	Allergic asthma
	Chronic rhinosinusitis with nasal polyposis (CRSwNP)
	Chronic idiopathic urticaria (CIU)
benralizumab (Fasenra Pen™) Policy	Asthma (severe)
mepolizumab (Nucala®)	Asthma (severe)
	Eosinophilic granulomatosis with polyangiitis
	Hypereosinophilic Syndrome
	Chronic Rhinosinusitis with Nasal Polyps
reslizumab (Cinqair®) Policy	Asthma (severe)

Policy Implementation/Update:

Action and Summary of Changes	Date
Added to PBO program	10/2023
Policy created	05/2023

Policy Type: PA/SP Pharmacy Coverage Policy: UMP158

Description

Tiopronin (Thiola) is an active reducing agent which undergoes thiol-disulfide exchange with cystine to form tiopronin-cystine disulfide, which is more water soluble than cystine. As a result, the amount of sparingly soluble cystine in the urine is decreased and the formation of cystine calculi is reduced.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
tiopronin (Thiola)	100 mg tablet	Nephrolithiasis (cystine), prevention	450 tablets/30 days
tiopronin (Thiola EC)	100 mg delayed release tablet		450 tablets/30 days
	300 mg delayed release tablet		150 tablets/30 days
generic tiopronin DR	100 mg delayed release tablet		450 tablets/30 days
	300 mg delayed release tablet		150 tablets/30 days

Initial Evaluation

I. **Tiopronin (Thiola; Thiola EC)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **OR**
      1. Younger than 18 years of age and weighing 20 kg or greater; **AND**
   B. Medication is prescribed by, or in consultation with, a nephrologist or urologist; **AND**
   C. If the request is for brand tiopronin (Thiola EC), treatment with generic tiopronin DR has been ineffective, not tolerated, or is contraindicated; **AND**
   D. A diagnosis of **severe homozygous cystinuria** when the following are met:
      1. Urinary cystine levels greater than 500 mg/day; **AND**
      2. Member has not been responsive to all of the following:
         i. High fluid intake
         ii. Urinary alkalinization
         iii. Diet modification (e.g. restriction of sodium and protein intake)

II. Tiopronin (Thiola; Thiola EC) is considered investigational when used for all other conditions.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms as indicated by a reduction in cystine stone production OR a urinary cystine concentration less than 250 mg/L.

Supporting Evidence

I. Tiopronin (Thiola; Thiola EC) is a reducing-agent that helps form tiopronin-cystine disulfide, which is more readily excreted by the body, as it is more water soluble.
II. Topronin (Thiola; Thiola EC) is FDA-approved to prevent cystine stone formation in adults and pediatric patients 20 kg and greater with severe homozygous cystinuria, who are unresponsive to high fluid intake, alkali, and diet modification.
III. The recommended initial dose in adult patients is 800 mg/day. In clinical studies, the average dose was about 1,000 mg/day.
IV. The recommended initial dose in pediatric patients 20 kg and greater is 15 mg/kg/day. Doses greater than 50 mg/kg per day should be avoided in pediatric patients. Pediatric patients receiving greater than 50 mg/kg tiopronin per day are at greater risk of proteinuria and nephrotic syndrome.
V. Tiopronin (Thiola; Thiola EC) tablets are not approved for use in pediatric patients weighing less than 20 kg as safety and efficacy has not been established in this population.
VI. Urinary cystine levels should be measured one month after initiation of tiopronin (Thiola; Thiola EC) and every three months thereafter. The dose should be adjusted to maintain a urinary cystine concentration of less than 250 mg/L.

Investigational or Not Medically Necessary Uses

I. Tiopronin (Thiola; Thiola EC) has not been sufficiently evaluated outside of severe homozygous cystinuria.

References

1. Thiola [prescribing information]. San Antonio, TX: Mission Pharmacal Company; June 2019.
2. Thiola EC [prescribing information]. San Antonio, TX: Mission Pharmacal Company; June 2019.
3. UpToDate, Inc. Cystine stones. UpToDate [database online]. Waltham, MA. Last updated March 01, 2019 Available at: http://www.uptodate.com/home/index.html.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added generic tiopronin to policy and required step through generic tiopronin prior to brand use	03/2024
Policy Created	12/2019

Policy Type: PA Pharmacy Coverage Policy: UMP229

Description

Tirbanibulin (Klisyri) is a topical microtubule inhibitor.

Length of Authorization

- Initial: One-time fill
- Renewal: Not eligible/Cannot be renewed

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
tirbanibulin (Klisyri)	2.5 mg/250 mg (1%) ointment in a single-dose packet	actinic keratosis (AK)	5 packets/5 days

Initial Evaluation

I. Tirbanibulin (Klisyri) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a dermatologist; **AND**
   C. Member has not been treated with tirbanibulin (Klisyri) before; **AND**
   D. A diagnosis of **actinic keratosis (AK)** when the following are met:
      1. Member will treat lesions on the face or scalp; **AND**
      2. Treatment with at least **TWO** of the following have been ineffective, not tolerated, or all are contraindicated:
         i. 5-fluorouracil (5-FU) cream
         ii. Imiquimod cream
         iii. Diclofenac gel

II. Tirbanibulin (Klisyri) is considered investigational when used for all other conditions, including but not limited to:
   A. Patients with recurrent AK previously treated with tirbanibulin (Klisyri)
   B. Treatment of AK on other body parts (e.g. hands, legs, neck, etc.) other than the face or scalp

Supporting Evidence

I. The safety and efficacy of tirbanibulin (Klisyri) has been studied in adult patients, with no clinical trial data to support the use in pediatric patients; however, AK is a skin condition generally seen in the older population.
II. AK is the most common precancer that forms on skin damaged by chronic exposure to ultraviolet (UV) rays from the sun or indoor tanning. Most AKs do not progress to squamous cell

carcinoma (SCC), but majority of cutaneous SCCs progress from AKs. Given AK may progress to SCC, dermatologist involvement in the patient's care is recommended.

III. Patients previously treated with tirbanibulin (Klisyri) were excluded from the clinical trials. The patients in the clinical trial only received one five-day treatment of tirbanibulin (Klisyri). The safety and efficacy of treating with a second application (i.e., treating AK that has recurred after treatment with tirbanibulin [Klisyri]) is unknown.

IV. The safety and efficacy of tirbanibulin (Klisyri) was studied in two identically designed Phase 3, double-blind, vehicle-controlled, randomized, parallel-group, multicenter studies in 702 patients with AK of the face or scalp.

- The majority of patients were white and male, with a Fitzpatrick skin type of I (pale white skin, blue/green eyes, blond/red hair) or II (fair skin, blue eyes) and a median of six lesions.
- The primary efficacy outcome was complete response rate and the main secondary outcome was partial response.

Outcomes	Trial 1 (N=351)		Trial 2 (N=351)		Pooled data (N=702)	
	tirbanibulin (N=175)	vehicle (N=176)	tirbanibulin (N=178)	vehicle (N=173)	tirbanibulin (N=353)	vehicle (N=349)
Complete response rate*	77 (44%)	8 (5%)	97 (54%)	22 (13%)	174 (49%)	30 (9%)
Difference	40% 95% CI (32-47); p <0.001		42% 95% CI (33-51); p <0.001		41% 95% CI (35-47); p <0.001	
Partial Response rate**	119 (68%)	29 (16%)	136 (76%)	34 (20%)	255 (72%)	63 (18%)
Difference	52% 95% CI (43-60); p <0.001		57% 95% CI (48-65); p <0.001		54% 95% CI (48-60); p <0.0001	

* Proportion of subjects achieving complete clearance of all AK in the selected area

** Proportion of subjects achieving reduction of at least 75% in the number of lesions within the application area

- Tirbanibulin (Klisyri) treated patients who achieved CR (N=174) were included in a one year follow up; of those, 124 (73%) patients developed lesions within the area treated with tirbanibulin (Klisyri). Out of the 124 patents, 72 (58%) had recurrent lesions and 52 (42%) had new lesions. The sustained complete clearance is 27%.
- The most common local reactions were erythema (91% of the patients) and flaking or scaling (82%). Although generally mild, crusting, swelling, vesiculation or pustulation, erosion, and ulceration were also seen.

V. Longstanding therapies for the treatment of AK include destructive therapies [e.g., surgery, cryotherapy, dermabrasion, photodynamic therapy (PDT)], field ablation treatments (e.g., chemical peels, laser resurfacing), and topical medications (e.g., fluorouracil, imiquimod, diclofenac).

- Topical medications including fluorouracil, imiquimod and diclofenac are used as first-line therapy with a well-established long-term efficacy and safety profile.
- In a randomized controlled trial comparing the recurrence of AKs after treatment with fluorouracil 5%, imiquimod 5%, or PDT, fluorouracil had the highest cumulative probability of remaining free from treatment failure (defined as <75% reduction in AK lesions) 12 months after treatment. For fluorouracil, 75% of patients were free from treatment failure, followed by imiquimod at 54%, PDT at 38%.
- Tirbanibulin (Klisyri) is a topical ointment applied once daily for five consecutive days. Patients who were previously treated with tirbanibulin (Klisyri) were excluded from the clinical trials. The patients in the clinical trial only received one five-day treatment cycle

of tirbanibulin (Klisyri) and had a high recurrence rate (73%) one year after treatment. There is limited data on long-term safety and efficacy.

Investigational or Not Medically Necessary Uses

I. Tirbanibulin (Klisyri) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Patients previously treated with tirbanibulin (Klisyri): Patients previously treated with tirbanibulin (Klisyri) were excluded from the clinical trials. The patients in the clinical trial only received one five-day treatment cycle of tirbanibulin (Klisyri). The safety and efficacy of treating more than one 25cm^2 area at a time or as a second application in an area with recurrence is unknown. There is no clinical trial data to support the use in patients previously treated.
   B. Treatment of AK on other body parts (e.g. hands, legs, neck, etc.) other than the face or scalp: The safety and efficacy of tirbanibulin (Klisyri) was studied in patients with AK of the face or scalp. No patients with lesions on other body parts were included in the clinical trial. There is no clinical trial data to support the use on other parts of the body.

References

1. Blauvelt A, Kempers S, Lain E, et al. Phase 3 Trials of Tirbanibulin Ointment for Actinic Keratosis. *N Engl J Med*. 2021;384(6):512-520. doi:10.1056/NEJMoa2024040.
2. R.N. Werner, et al. Evidence- and consensus-based (S3) Guidelines for the Treatment of Actinic Keratosis – International League of Dermatological Societies in cooperation with the European Dermatology Forum. EADV 2015, 29, 2069–2079 DOI: 10.1111/jdv.13180
3. Maud H.E. Jansen, M.D., et al. Randomized Trial of Four Treatment Approaches for Actinic Keratosis. N Engl J Med 2019; 380:935-946 DOI: 10.1056/NEJMoa1811850
4. Actinic keratosis: Diagnosis and treatment. Retrieved February, 2021, from https://www.aad.org/public/diseases/skin-cancer/actinic-keratosis-treatment
5. de Oliveira ECV, et al. Actinic keratosis - review for clinical practice. Int J Dermatol. 2019;58(4):400-407.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP230

Description

Tivozanib (Fotivda) is an orally administered VEGFR kinase inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
tivozanib (Fotivda)	1.34 mg capsules	Relapsed or refractory advanced renal cell carcinoma, following at least two prior systemic therapies	21 capsules/28 days
	0.89 mg capsules		

Initial Evaluation

I. **Tivozanib (Fotivda)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. Not used in combination with any other oncology therapy (e.g., everolimus [Afinitor], temsirolimus (Torisel), ipilimumab [Yervoy], nivolumab [Opdivo]; **AND**
   D. A diagnosis of **advanced or metastatic renal cell carcinoma** when the following are met:
      1. Provider attestation the member has clear cell component histology; **AND**
      2. Member has renal cell carcinoma that is relapsed or refractory to at least **TWO** prior systemic therapies (e.g., axitinib [Inlyta], ipilimumab [Yervoy], nivolumab [Opdivo], everolimus [Afinitor]; **AND**
         i. At least **ONE** of the prior therapies is an anti-VEGFR TKI (e.g., axitinib [Inlyta], lenvatinib [Lenvima], pazopanib [Votrient], sunitinib [Sutent], cabozantinib [Cabometyx].

II. Tivozanib (Fotivda) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Renal cell carcinoma prior to third-line treatment

III. Tivozanib (Fotivda) is considered investigational when used for all other conditions, including but not limited to:
   A. Renal cell carcinoma in combination with other oncolytic therapies

B. Renal cell carcinoma prior to the relapsed refractory and/or advanced settings
C. Prostate cancer
D. Breast cancer
E. Ovarian, fallopian tube, or primary peritoneal cancer
F. Lung Cancer
G. Gastrointestinal tumors
H. Hepatocellular carcinoma
I. Cholangiocarcinoma
J. Colorectal cancer
K. Glioblastoma

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Provider attestation the medication will not be used in combination with any other oncology therapy (e.g., everolimus [Afinitor], temsirolimus (Torisel), ipilimumab [Yervoy], nivolumab [Opdivo]; **AND**
IV. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread.

Supporting Evidence

I. Tivozanib (Fotivda) is a VEGFR tyrosine kinase inhibitor (TKI) that is FDA-approved for patients with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more systemic therapies. Tivozanib (Fotivda)is approved for 21 days on therapy and seven days off until disease progression or unacceptable toxicity. It is the first therapy specifically FDA-approved for the third-line setting, but joins several other anti-VEGFR medications for this condition, as well as immunotherapies and mTOR inhibitors. All therapy categories are utilized in the subsequent treatment setting after members have progressive disease.
II. Other anti-VEGFR medications include: cabozantinib (Cabometyx), pazopanib (Votrient), sorafenib (Nexavar), lenvatinib (Lenvima), sunitinib (Sutent) and axitinib (Inlyta). Immunotherapy options include: ipilimumab (Yervoy), nivolumab (Opdivo), avelumab (Bavencio). The mTOR inhibitors include therapies such as everolimus (Afinitor), temsirolimus (Torisel). Often, immunotherapies will be used in combination with each other, or in combination with anti-VEGFR medications. The mTOR inhibitors are also utilized in combination with anti-VEGFR medications; however, use of two concomitant anti-VEGFR medications has not been evaluated, and given the unfavorable safety profiles of these medications, combination treatment is not advised.
III. As of March 2021, all three categories of medications are used for clear cell RCC. In the subsequent treatment setting, NCCN Cat. 1 recommended regimens include cabozantinib

(Cabometyx), nivolumab (Opdivo), axitinib (Inlyta), and lenvatinib (Lenvima) plus everolimus (Afinitor). The remainder have Cat. 2A recommendations, with the exception of sorafenib (Nexavar) which has a Cat. 2B recommendation.

IV. Treatment choice is based on stage of disease, prognosis, line of therapy, and other patient characteristics. Tolerability and safety considerations are taken into account for treatment choice as well. Given the extensive treatment options, combinations, and unfavorable safety profiles that require extensive medication monitoring, medication should be prescribed by or in consultation with a specialist.

V. In 2013 tivozanib (Fotivda) was evaluated in a Phase 3 trial vs. sorafenib (Nexavar) in 517 patients with RCC for initial targeted therapy in those that had received up to one prior systemic treatment. Patients had prior nephrectomy, clear cell RCC, and up to one prior therapy that was not an anti-VEGFR. Progression-free survival (PFS) was statistically significant favoring tivozanib (Fotivda); however, the overall survival (OS) was not statistically different. In 2013, the FDA issued a Complete Response Letter to Aveo, given an inconclusive risk benefit assessment and required another trial from the manufacturer in the advanced setting.

VI. Following the CRL, tivozanib (Fotivda) was evaluated in an open-label, randomized, Phase 3 trial vs. sorafenib (Nexavar) in 350 adults with RCC. Ninety-eight percent of patients had clear cell histology. Patients had advanced disease and were relapsed or refractory to two or three prior systemic therapies, including at least one anti-VEGFR therapy. Forty-five percent of patients had two prior anti-VEGFR therapies and 26% had prior checkpoint inhibitor therapy. About 60% of patients had intermediate, 20% had favorable, and 20% had poor prognoses. The study showed a statistical increase in PFS (5.6 months vs. 3.9 months), as well as partial responses (18% vs. 8%); however, OS was not statistically different and numerically favored sorafenib (Nexavar). To date, tivozanib (Fotivda) has not proven to have clinically meaningful outcomes such as increased survival, improvement in quality of life or symptom control. This is similar for the comparator, sorafenib (Nexavar). Thus, clinical benefit of either therapy remains unclear.

VII. To date, the safety tivozanib (Fotivda) is similar to other anti-VEGFR medications. Serious adverse events (AE) occurred in 11% of patients on tivozanib (Fotivda) and in 10% for sorafenib (Nexavar). AE more frequent with tivozanib (Fotivda): hypertension (44% vs. 31%), bleeding (17% vs. 12%), nausea (30% vs. 18%), decreased appetite (39% vs. 30%), dysphonia (27% vs. 9%), cough (22% vs. 15%), and hypothyroidism (24% vs. 11%). AE more frequent with sorafenib (Nexavar): diarrhea (54% vs. 44%), rash (52% vs. 18%), and palmar-plantar syndrome (41% vs. 16%). Stomatitis, vomiting, pain, dyspnea, and weight loss were common and occurred in similar rates between treatment arms

VIII. Dose interruption due to AE occurred in 48% of the tivozanib (Fotivda) group and 63% of the sorafenib (Nexavar) group. Dose reductions due to AE occurred in 24% for tivozanib (Fotivda) and 38% for sorafenib (Nexavar). The lower dose reduction and interruption rates for tivozanib (Fotivda) are likely attributable to the seven-day break within each cycle vs. continuous dosing with sorafenib (Nexavar). Given lack of long-term safety evaluation and lack of evaluation against placebo, true benefits and harms are unknown at this time. At this time there is insufficient safety information (given limited patient experience and duration of therapy) to definitively indicate that there is substantial safety differences between any of the anti-VEGFR therapies.

Investigational or Not Medically Necessary Uses

I. Tivozanib (Fotivda) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Renal cell carcinoma prior to third-line.
      i. Tivozanib (Fotivda) has been evaluated for first-line and second-line treatment but did not achieve FDA-approval given uncertain risks and benefits.
   B. The following indications have not been sufficiently studied for efficacy and use outside of clinical trials is not advised given the unfavorable safety profile alone or in combination with other medications:
      i. Renal cell carcinoma in combination with other oncolytic therapies
      ii. Renal cell carcinoma prior to the relapsed refractory and/or advanced settings
      iii. Prostate cancer
      iv. Breast cancer
      v. Ovarian, fallopian tube, or primary peritoneal cancer
      vi. Lung Cancer
      vii. Gastrointestinal tumors
      viii. Hepatocellular carcinoma
      ix. Cholangiocarcinoma
      x. Colorectal cancer
      xi. Glioblastoma

References

1. Fotivda [Prescribing Information]. Aveo Pharmaceuticals Inc. Boston, MA. March 2021.
2. Rini BI, Pal SK, Escudier BJ, et al. Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): a phase 3, multicentre, randomized, controlled, open-label study. *Lancet Oncol*. 2020;21(1):95-104.
3. Motzer RJ, Nosov D, Eisen T, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. *J Clin Oncol*. 2013;31(30):3791-3799.
4. NCCN Guidelines for the Treatment of Kidney Cancer. V.2.2021. Updates February 3, 2021.
5. Powles T, ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Recent eUpdate to the ESMO Clinical Practice Guidelines on renal cell carcinoma on cabozantinib and nivolumab for first-line clear cell renal cancer: Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021;32(3):422-423

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP159

Tobramycin (TOBI®) inhalation solution, generic tobramycin inhalation solution, tobramycin (KITABIS™) inhalation solution, tobramycin (TOBI Podhaler®) inhalation solution and tobramycin (Bethkis®) inhalation solution are aminoglycoside antibacterial drugs that act primarily by disrupting protein synthesis in the bacterial cell which eventually leads to death of the cell. Tobramycin inhalation solutions have activity against a wide range of gram-negative bacteria including *Pseudomonas aeruginosa*.

Length of Authorization

- Initial:
  - i. Non-Cystic Fibrosis Chronic Bronchiectasis: 6 months (3 fills)
  - ii. Cystic Fibrosis with *Pseudomonas aeruginosa:* 12 months (7 fills per year)
- Renewal:
  - i. Non-Cystic Fibrosis Chronic Bronchiectasis: None, initial criteria applies
  - ii. Cystic Fibrosis with *Pseudomonas* aeruginosa: 12 months (7 fills per year)

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
tobramycin (TOBI)	Cystic fibrosis with P*seudomonas aeruginosa* Non- cystic fibrosis Chronic Bronchiectasis	300 mg/5mL one single-use ampule	56 single-dose ampules/28 days
generic tobramycin inhalation solution		300 mg/5mL one single-use ampule	56 single-dose ampules/28 days
tobramycin (KITABIS)		300 mg/5mL one single-use ampule	56 single-dose ampules/28 days
tobramycin (Bethkis)		300 mg/4 mL one single-use ampule	56 single-dose ampules/28 days
tobramycin (TOBI Podhaler)		28mg inhalation capsule	224 inhalation capsules /28 days

Initial Evaluation

I. **Generic tobramycin inhalation solution** may be considered medically necessary when the following criteria below are met:
   A. Member is six years of age or older for a diagnosis of cystic fibrosis; **OR**
      1. Member is 18 years of age or older for a diagnosis of chronic bronchiectasis; **AND**
   B. Medication is prescribed by, or in consultation with, a pulmonologist; **AND**
   C. A diagnosis of **cystic fibrosis** when the following are met:
      1. Member has tested positive for *Pseudomonas aeruginosa* in the lungs; **AND**
      2. Member has a documented baseline FEV_1 percentage (this may be used in renewal at a later date); **AND**
      3. Member is <u>not</u> colonized *with Burkholderia cepacia*; **OR**
   D. A diagnosis of **chronic bronchiectasis** when the following are met:

1. Member has tested positive for *Pseudomonas aeruginosa* in an airway culture (e.g., lungs, sputum, nasopharyngeal) for initial treatment OR re-infection; **AND**
2. Member has had at least two exacerbations in the last 12 months that have required acute antibiotic treatment (10-14 days in length); **AND**
3. Member has failed long-term oral antibiotic treatment (e.g., ciprofloxacin, levofloxacin, moxifloxacin, azithromycin, sulfamethoxazole/trimethoprim)

II. **Tobramycin (TOBI) inhalation solution, tobramycin (KITABIS) inhalation solution, tobramycin (BETHKIS) inhalation solution and tobramycin (TOBI Podhaler) inhalation solution** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(D) above are met; **AND**
   B. Treatment with generic tobramycin inhalation solution has been ineffective, contraindicated, or not tolerated.

III. Generic tobramycin inhalation solution, tobramycin (KITABIS) inhalation solution, tobramycin (TOBI) inhalation solution, tobramycin (BETHKIS) inhalation solution and tobramycin (TOBI Podhaler) inhalation solution are considered investigational when used for all other conditions, including but not limited to:
   A. Non–cystic fibrosis chronic bronchiectasis with another bacterial culture outside of *Pseudomonas aeruginosa*

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member has a diagnosis of Cystic Fibrosis with *Pseudomonas aeruginosa;* **AND**
III. Member has exhibited improvement or stability of disease symptoms (i.e., stabilization or improvement of FEV1, reduced number of respiratory-related hospitalizations or reduced exacerbations).

Supporting Evidence

I. Due to the complexity of the disease states of the policy, tobramycin inhalation solution needs to be prescribed by, or in consultation with, a pulmonologist or an infectious disease specialist.
II. For the treatment of Cystic Fibrosis, the safety and efficacy of tobramycin inhalation solution in pediatric patients under six years of age has not been established due to the lack of clinical trial data. The use is not indicated in pediatric patients under the age of six.
   - Tobramycin inhalation solution is administered twice daily in alternating periods of 28 days to help prevent resistance to tobramycin and offset potential adverse events (ADE). After 28 days of therapy, patients should stop tobramycin therapy for the next 28 days, and then resume therapy for the next “28 days on/28 days off” cycle. To ensure appropriate dosing of tobramycin nebulizer or podhaler in members with cystic fibrosis, approval will allow for 7 fills within a one year approval period.

- Safety and efficacy have not been demonstrated in patients with FEV1 <40% or >80% (Bethkis), FEV1 <25% or >80% (Tobi Podhaler), FEV1 <25% or >75% (Tobi and Kitabis), or patients colonized with Burkholderia cepacia. However, real world application does suggest value in patients outside these ranges as some patients may have low FEV1 values, but still have good quality of life with regular jobs, travel, and limited oxygen use for sleep versus other patients who may have FEV1 over 40 and still require oxygen around the clock, unable to work on disability. Therefore, a documented FEV1 is required from baseline as use of tobramycin is used to maintain or improve FEV1 and renewal criteria reflects this ask.
- Guidelines developed by the Pulmonary Therapies Committee of the Cystic Fibrosis Foundation made the following recommendations for tobramycin solution for inhalation (TSI) (written prior to the approval of aztreonam lysine inhalation solution (AZLI)):
    - Moderate to severe lung disease (>6 years of age): For patients colonized with P. aeruginosa, the chronic use of TSI is strongly recommended to improve lung function and reduce exacerbations (grade A recommendation).
    - Mild lung disease or asymptomatic (>6 years of age): For patients colonized with P. aeruginosa, the chronic use of TSI is recommended to reduce exacerbations (grade B recommendation).

III. For the treatment of chronic bronchiectasis, safety and efficacy has not been established in pediatric patients, those under 18 years of age.

- Chronic infection is a hallmark in bronchiectasis; the US Bronchiectasis Research Registry reported 1826 patients with bronchiectasis with the most common organism found causing the infection to be *Pseudomonas aeruginosa* (33%). The majority of patients, with normal lung function tests (i.e., forced vital capacity, FVC), are able to clear this infection with antibiotics, while those with impaired lung function are unable to. When the patient has frequent exacerbations (three or more a year), targeted chronic antibiotic strategies may be helpful in reducing exacerbations and improving quality of life.
- The fluoroquinolone family is typically used first line for both acute and chronic bronchiectasis, macrolide use also is supported for those with allergies. Both classes have demonstrated benefit versus placebo in regard to reducing frequency of exacerbations. Chronic dosing may look like azithromycin 250mg three times a week which can be increased according to clinical response or adverse events or ciprofloxacin twice daily.
- The British Thoracic Society guidelines give the clearest step wise approach to care calling for steps one and two being treatment of underlaying causes, pulmonary rehabilitation, and acute antibiotic use (mainly oral), before moving into step three where patients are having exacerbations despite prevention care. Patients are then recommended to undergo pathogen testing and recommended either long term macrolides or inhaled tobramycin, or a combination of both should patients still continue to have worsening symptoms. Intravenous (IV) antibiotics are more reserved for those patients with continued hospitalization despite all of the above.

UpToDate also holds IV use for those acutely critically ill, or those with known antibiotic resistance.

- Inhaled antibiotics, such as tobramycin, have been used in the refractory setting, mainly in those with chronic infection of *Pseudomonas aeruginosa*. However, studies have not shown consistent benefit.
    i. Drobnic et al. 2005: double-blind, placebo-controlled, crossover study randomized 30 patients to initial tobramycin inhaled solution (TIS) 300 mg or placebo BID for 6 months, followed by a one-month washout period and 6 months of therapy with the other treatment. 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 hospital admissions (0.15 vs. 0.75; P = 0.038) and fewer days of admission (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.
    ii. Barker et al. 2000: randomized, double-blind, placebo-controlled study, patients received either TIS 300 mg (n = 37) or placebo (n = 37) twice daily for 4 weeks and were followed for an additional 2 weeks off treatment. At Week 4, the TIS group had a mean decrease in *P. aeruginosa* density of 4.54 log10 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 showed an improved condition. Mean percent change in FEV1 percent predicted from Week 0 to Week 4 was similar for the TIS and placebo groups (P = 0.41)
    iii. Orriols et al. 2015: 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. Median time to recurrence of *P. aeruginosa* infection was higher in TIS group than in the placebo group (P = 0.048). At the end of the study 54.5% of the patients were free of *P. aeruginosa* in the tobramycin group (n = 6/11) and 29.4% in the placebo group (n = 5/17). The numbers of exacerbations (1.27 vs. 2.5; P = 0.044), hospital admissions (0.06 vs. 0.47; P = 0.037) and days of hospitalization (0.9 vs. 13.56; P = 0.034) were lower in the tobramycin than in the placebo group. No significant difference was found in pulmonary function tests.
    iv. The BATTLE study was a randomized, double-blind, placebo-controlled study in the Netherlands of adult patients treated with tobramycin inhaled solution (TIS) once daily (n=26) or placebo daily (n=26) for 52 weeks with a primary outcome of a yearly rate of pulmonary exacerbations. Those in the TIS group had 41 exacerbations over the year compared to 58 in the placebo group. At the end of the study, no pathogens were in the sputum of 10 patients the TIS group versus four of the placebo group.

v. The iBEST study was the largest study with 107 total patients randomized 1:1:1 to receive TIS daily at three different doses (84, 140, or 224mg) and within each group the patients either received continuous TIS or cyclic TIS [28 days on/28 days off] or placebo). All patients were adults. The primary endpoint was change in *P. aeruginosa* sputum density. Each group met statistical significance versus placebo, with 224mg achieving the best change in density. Additionally, those receiving cyclic TIS versus continuous dosing schedule also achieved higher clearance, but this was only significant in the 224mg branch and not in the lower doses.

- The society guidelines vary in their position on tobramycin in the treatment of chronic bronchiectasis. The European Respiratory Society and the British Thoracic guidelines have incorporated tobramycin into the treatment of chronic bronchiectasis, where the United States guidelines are not updated to include this. These guidelines recommend a therapeutic trial of inhaled antibiotics in patients with three or more exacerbations a year or significant morbidity from fewer exacerbations and *Pseudomonas aeruginosa* in their sputum; however, the clinical trials widely included those with only two. Our criteria reflects two so we are able to catch moderately affected patients and hopefully prevent additional hospitalizations.
- Due to the variability of the time frames of the clinical trial, we have gone with cyclic dosing as recommended via the iBEST trial with dosing of 300mg TIS twice daily due to the highest clearance of *P. aeruginosa* in the treatment arms and the collected knowledge from the other trials that as low as one month of treatment reduced exacerbations. Additionally, there is not a clear consensus to how many months of therapy patients require, so we are allowing six months for three rounds of therapy without refills to where the patient would be required to meet initial criteria on the next occurrence. This is also to avoid undue adverse events as each clinical trial was associated with higher ADE in the TIS arms than placebo with varying discontinuation rates due to these adverse events.
- The body of evidence overall is lacking in robustness of data. The clinical programs looking at this use were under powered or met surrogate endpoints, example eradicating *P. aeruginosa,* but did not consistently impact time to next exacerbation or increased actual lung function, and there was an increased number of adverse effects from the medication itself. There was a lower number of hospitalizations, which is a positive quality of life piece for the patients, but this is not a correlation in improvements to the disease itself.

IV. In the absence of direct comparative trails there's no evidence to conclude that one product is safer or more effective than another.

Investigational or Not Medically Necessary Uses

I. Non–cystic fibrosis chronic bronchiectasis for treatment of acute exacerbations OR those not colonized with *Pseudomonas aeruginosa*

References

1. KITABIS PAK [Prescribing Information] Catalent Pharma Solutions, LLC Woodstock, IL 60098. 8/2021
2. TOBIPodhaler [Prescribing Information]Novartis Pharmaceuticals Corporation 2/2023
3. TOBI inhalation solution [Prescribing Information]. Novartis Pharmaceuticals Corporation 4/2020
4. Bethkis inhalation solution [Prescribing Information]. Chiesi USA, Inc 12/2019
5. Barker, A. F. (n.d.). Treatment of bronchiectasis in adults. Retrieved from https://www-uptodate.com.liboff.ohsu.edu/contents/treatment-of-bronchiectasis-in-adults?search=tobramycin in Non–cystic fibrosis bronchiectasis&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2#H23
6. Bilton, D., Henig, N., Morrissey, B., & Gotfried, M. (n.d.). Addition of Inhaled Tobramycin to Ciprofloxacin for Acute Exacerbations of Pseudomonas aeruginosa Infection in Adult Bronchiectasis. CHEST, 130(5), 1503–1510. doi: https://doi.org/10.1378/chest.130.5.1503
7. Mogayzel PJ Jr, Naureckas ET, Robinson KA, M, et al. Pulmonary Clinical Practice Guidelines Committee. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2013 Apr 1;187(7):680-9. doi: 10.1164/rccm.201207-1160oe. PMID: 23540878. Reaffirmed July 2021.
8. Orriols R, Hernando R, Ferrer A, Terradas S, Montoro B. Eradication Therapy against Pseudomonas aeruginosa in Non-Cystic Fibrosis Bronchiectasis. Respiration. 2015;90(4):299-305. doi: 10.1159/000438490. Epub 2015 Sep 5. PMID: 26340658.
9. 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 Aug;162(2 Pt 1):481-5. doi: 10.1164/ajrccm.162.2.9910086. PMID: 10934074.
10. Drobnic ME, Suñé P, Montoro JB, et al. Inhaled tobramycin in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection with Pseudomonas aeruginosa. Ann Pharmacother. 2005 Jan;39(1):39-44. doi: 10.1345/aph.1E099. Epub 2004 Nov 23. PMID: 15562142.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy

Policy Name	Disease state
Cystic Fibrosis, CFTR Modulators	Cystic Fibrosis
dornase alfa (Pulmonzyme)	
mannitol (Bronchitol)	
aztreonam (Cayston)	

Policy Implementation/Update:

Action and Summary of Changes	Date
Edited FEV1 in criterion setting of CF to remove specific values. Updates to supporting evidence. Added in criteria for coverage for non-CF bronchiectasis per request of UMP as well as updated supporting evidence for this addition. Formatting updates.	06/2023
Removed step through tobramycin (BETHKIS) inhalation solution and tobramycin (KITABIS) inhalation solution	12/2021
• Updated criteria to policy format • Tobramycin (TOBI Podhaler) inhalation solution is considered medically necessary if treatment with tobramycin (KITABIS) inhalation solution and tobramycin (TOBI) inhalation solution has been ineffective, contraindicated, or not tolerated • Tobramycin (TOBI) inhalation solution and tobramycin (BETHKIS) inhalation solution are considered medically necessary if treatment with tobramycin (KITABIS) and generic tobramycin has been ineffective, contraindicated or not tolerated • Added tobramycin (KITABIS) to policy	12/2019
Previous Reviews	03/2013; 03/2017;

Policy Type: PA/SP Pharmacy Coverage Policy: UMP068

Description

Tolvaptan (Jynarque) is a selective vasopressin V(2)-receptor antagonist.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
tolvaptan (Jynarque)	15 mg tablets	Autosomal dominant polycystic kidney disease	28 tablets/28 days
	30 mg tablets		60 tablets/30 days
	15 & 15 mg tablet therapy pack		56 tablets/28 days (1 box/28 day)
	30 & 15 mg tablet therapy pack		56 tablets/28 days (1 box/28 day)
	45 & 15 mg tablet therapy pack		56 tablets/28 days (1 box/28 day)
	60 & 30 mg tablet therapy pack		56 tablets/28 days (1 box/28 day)
	90 & 30 mg tablet therapy pack		56 tablets/28 days (1 box/28 day)

Initial Evaluation

I. Tolvaptan (Jynarque) may be considered medically necessary when the following are met:
   A. Prescribed by prescribed by, or, in consultation with a nephrologist; **AND**
   B. A diagnosis of **autosomal dominant polycystic kidney disease (ADPDK)** when the following are met:
      1. Diagnosis is confirmed by imaging (e.g., ultrasound, CT, MRI) or genetic test; **AND**
      2. Member has rapidly-progressing ADPKD (e.g., reduced or declining renal function, high or increasing total kidney volume [height adjusted]); **AND**
      3. Member does not have Stage 5 chronic kidney disease (CKD) defined as a glomerular filtration rate {GFR} < 15 mL/min/1.73 m2, or receiving dialysis

II. Tolvaptan (Jynarque) is considered investigational when used for all other conditions, including but not limited to:
   A. Hyponatremia

Renewal Evaluation

I. Member experienced disease stability, or improvement (e.g., reduction in number and/or rate of cyst production, change in renal function, reduction in rate of total kidney volume growth, slowed rate of kidney function decline); **AND**
II. Documented lack of unacceptable toxicity

Supporting Evidence

I. Polycystic kidney disease (PKD) includes inherited diseases that cause irreversible decline in kidney function. PKD may be inherited as an autosomal dominant or recessive trait. The autosomal dominant form (autosomal dominant PKD [ADPKD]) is the most common genetic cause of chronic kidney disease (CKD). The majority of individuals with PKD eventually require renal replacement therapy.
II. The diagnosis of ADPKD is most commonly made via screening using ultrasound, CT scan or MRI. Genetic testing is available for definitive diagnosis, but is rarely performed. Confirmed diagnosis of ADPKD via one of these tests is required prior to coverage of Jynarque.
III. Tolvaptan (Jynarque) was shown to slow the rate of decline in renal function in adults at risk of rapidly-progressing ADPKD in two phase 3 randomized controlled trials, TEMPO and REPRISE.
    - TEMPO: Included 1445 adult patients with estimated creatinine clearance >60 mL/min and total kidney volume (TKV) >750 mL. The trial met the pre-specified primary endpoint of 3-year change in TKV ($p<0.0001$). The annual decline in eGFR was slower among patients who received tolvaptan compared to placebo (-2.72 versus -3.70 mL/min/1.73 m2 per year). Tolvaptan also reduced the rate of decline in kidney function at three years (hazard ratio [HR] 0.39, 95% CI 0.26-0.57), and the incidence of clinically significant kidney pain (HR 0.64, 95% CI 0.47-0.89).
    - REPRISE: Examined the effect of tolvaptan in patients with ADPKD who had reduced eGFR; such patients were generally not included in the TEMPO trial. At 12 months, the change from baseline eGFR was lower among those assigned tolvaptan as compared with placebo (-2.34 versus -3.61 mL/min/1.73 m^2); the group difference was 1.27 mL/min/1.73 m^2 (95% CI 0.86-1.68).
    - The analysis of the REPRISE trial, and a post-hoc analysis of the TEMPO trial, showed that tolvaptan (Jynarque) may extend the time until stage 5 CKD (ie, eGFR <15 mL/min/1.73 m2) from six to nine years among patients who start tolvaptan with an eGFR <60 mL/min/1.73 m2, and, even longer among those who start tolvaptan earlier.
    - Clinical trial criteria for rapidly progressive ADPKD
        i. Age 18-50 AND eGFR ≥60ml/min/1.73m2 AND Total Kidney Volume ≥750ml
        ii. Age 18-55 AND eGFR 25 to 65ml/min/1.73m2
        iii. Age 56-65 AND eGFR 25 to 44 ml/min/1.73m2 AND documented eFGR decline of more than 2.0 ml/min/1.73m2 per year
    - The pivotal trials for Jynarque did not involve patients with Stage 5 CKD (glomerular filtration rate [GFR] < 15 mL/min/1.73 m2 or receiving dialysis).
IV. Tolvaptan (Jynarque) is a part of a Risk Evaluation and Mitigation Strategy (REMS) program to monitor for liver injury.

V. Tolvaptan (Jynarque) should not be used off-label for other diagnoses due to lack of evidence, and risk of adverse events.

VI. In clinical trials, outcomes included the reduction in rate of total kidney volume growth, the slowed rate of kidney function decline, improvement in renal function, a change in mean arterial blood pressure, and change in renal pain. Stability of disease, or improvement in at least one of these measures, is indicative of treatment response. Additionally, fatal liver injury is a significant safety concern of Jynarque; liver function tests should be monitored periodically.

Investigational or Not Medically Necessary Uses

I. Hyponatremia
   A. Samsca, is a tolvaptan formulation that is FDA approval for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium of less than 125 mEq/L or less marks hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure and syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Jynarque has not been evaluated for treatment of hyponatremia.

References

1. Jynarque [Prescribing Information]. Tokyo, Japan: Otsuka Pharmaceutical Co. April 2018
2. Muto S. Kawano H., Higashihara E., et al. The effect of tolvaptan on autosomal dominant polycystic kidney disease patients: a subgroup analysis of the Japanese patient subset from TEMPO 3:4 trial. Clin Exp Nephrol. 2015;19(5):867-877.
3. Torres, VE, Chapman, AB, Devuyst, O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. The New England journal of medicine. 2012 Dec 20;367(25):2407-18. PMID: 23121377
4. Torres VE., Chapman AB., Devuyst O., et al. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. N Engl J Med. 2017;377:1930-1942.
5. UpToDate, Inc. Treatment of autosomal dominant polycystic kidney disease. UpToDate [database online]. Waltham, MA. Available at http://www.uptodate.com/home/index.html. Updated April 12, 2019

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated to policy format. Added the following: quantity limits for new 15 mg and 30 mg tablet, therapy to be prescribed by or in consultation with nephrologist, limited use to reflect patient population included in clinical trial (i.e. rapidly progressing ADPKD and do not have stage 5 CKD).	5/2019
Date created	05/2018

Policy Type: PA/SP Pharmacy Coverage Policy: UMP099

Description

Tolvaptan (Samsca) is an orally administered vasopressin V2-receptor antagonist which causes an increase in urine water excretion that results in an increase in free water clearance (aquaresis), a decrease in urine osmolality, and a resulting increase in serum sodium concentrations.

Length of Authorization

- Initial: one month
- Renewal: no renewal

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
tolvaptan (Samsca)	15 mg tablet	Hypervolemic or euvolemic hyponatremia	30 tablets/30 days*
	30 mg tablet		60 tablets/30 days*

*****_Therapy should not be continued past 30 days._

Initial Evaluation

I. Tolvaptan (Samsca) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an endocrinologist or nephrologist; **AND**
   C. Medication was initiated in the hospital; **AND**
   D. The requested treatment course will not exceed a 30-day duration per FDA recommendation; **AND**
   E. A diagnosis of **clinically significant hypervolemic or euvolemic hyponatremia** when the following are met:
      1. Serum sodium is less than 125 mEq/L; **OR**
      2. Serum sodium is greater than 125 mEq/L **and** patient has symptomatic hyponatremia (e.g., nausea, vomiting, headache, lethargy, confusion) that has resisted correction with fluid restriction

II. Tolvaptan (Samsca) is considered investigational when used for all other conditions, including but not limited to:
   A. Autosomal Dominant Polycystic Kidney Disease (ADPKD)
   B. Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms

Supporting Evidence

I. Per the label, tolvaptan (Samsca) 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 and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).
II. Safety and effectiveness of tolvaptan (Samsca) in pediatric patients has not been established.
III. Per the label, patients should be in a hospital for initiation and re-initiation of therapy to evaluate the therapeutic response and because too rapid correction of hyponatremia can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma and death.
IV. To minimize the risk of liver injury, tolvaptan (Samsca) should not be administered for more than 30 days. Based largely on the hepatic injury noted in the TEMPO trial, on April 2013 the FDA recommended that: "treatment should be stopped if the patient develops signs of liver disease. Treatment duration should be limited to 30 days or less, and use should be avoided in patients with underlying liver disease, including cirrhosis".
V. It has not been established that raising serum sodium with tolvaptan (Samsca) provides a symptomatic benefit to patients.

Investigational or Not Medically Necessary Uses

I. Autosomal Dominant Polycystic Kidney Disease (ADPKD)
    A. Jynarque (tolvaptan) is another tolvaptan product that is indicated to slow kidney function decline in adults at risk of rapidly-progressing ADPKD; however, the recommended dosing in Jynarque differs from the Samsca product. Per the tolvaptan (Samsca) label, because of the risk of hepatotoxicity, tolvaptan should not be used for ADPKD outside of the FDA-approved REMS.
II. Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms.
    A. Tolvaptan (Samsca) has not been studied in a setting of urgent need to raise serum sodium acutely.

References

1. Samsca [prescribing information]. Rockville, MD: Otsuka Pharmaceuticals; April 2018.
2. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med. 2012;367(25):2407-18.
3. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Verbalis JG, Goldsmith SR, Greenberg A,Korzelius C, Schrier RW, Sterns RH, Thompson CJ. https://pubmed.ncbi.nlm.nih.gov/24074529/Am J Med. 2013;126:0.3. Spasovski G, Vanholder R, Allolio B, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Neprhol DialTransplant 2014; 29 Suppl 2:i1.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP247

Description

Tralokinumab (Adbry) is a subcutaneous fully human monoclonal antibody of interleukin-13 (IL-13).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
tralokinumab (Adbry)	150 mg prefilled syringe	Moderate-to-Severe Atopic Dermatitis	**First Month:** 6 syringes/28 days **Maintenance:** 4 syringes/28 days *300 mg (2 syringes)/28 days may be considered for patients under 100 kg who achieve clear skin*

Initial Evaluation

I. **Tralokinumab (Adbry)** may be considered medically necessary when the following criteria are met:
   A. Member is 12 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a dermatologist or allergist; **AND**
   C. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat atopic dermatitis or another auto-immune condition (e.g. Otezla, Xeljanz, Olumiant); **AND**
   D. A diagnosis of **moderate-to-severe atopic dermatitis** when the following are met:
      1. Body surface area (BSA) involvement of at least 10%; **OR**
         i. Involves areas of the face, ears, hands, feet, or genitalia; **AND**
      2. Treatment with at least **TWO** of the following groups has been ineffective or not tolerated, or **ALL** are contraindicated:
         i. Group 1: topical corticosteroids of at least medium/moderate potency (e.g., clobetasol, betamethasone, halobetasol)
         ii. Group 2: topical calcineurin inhibitors (e.g., tacrolimus ointment, pimecrolimus cream)
         iii. Group 3: topical PDE-4 inhibitor (crisaborole [Eucrisa]); **AND**
      3. Treatment with dupilumab (Dupixent) and upadacitinib (Rinvoq) have been ineffective, contraindicated, or not tolerated.

II. Tralokinumab (Adbry) is considered investigational when used for all other conditions, including but not limited to:
   A. Asthma or COPD
   B. Nasal polyps
   C. Pediatric or adolescent atopic dermatitis
   D. Ulcerative colitis
   E. Alopecia areata

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat atopic dermatitis or another auto-immune condition (e.g. Otezla, Xeljanz, Olumiant); **AND**
IV. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in IGA score from baseline, BSA involvement, pruritis symptoms)

Supporting Evidence

I. Atopic dermatitis (AD), also known as atopic eczema, is an inflammatory skin condition most frequently occurring in pediatric patients. It manifests with pruritis, dry skin, crusting, and serous oozing causing chronic scratching which leads to blister formation, skin thickening (lichenification), fissuring, or lesions. This condition is associated with elevated serum IgE and it is often a comorbid condition with asthma and allergic conditions.
II. Treatments for mild-to-moderate AD include topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), phototherapy, and/or crisaborole (Eucrisa) – a PDE4 inhibitor. Symptomatic treatments include oral and topical antihistamines and sleep aids for nighttime pruritus. Treatment choice between these products is dependent on severity, location, and other patient specific factors (e.g., allergies, age). According to AAD guidelines, TCIs may be preferable to TCS in patients with recalcitrance to steroids, sensitive areas involved, steroid-induced atrophy, and long-term uninterrupted topical steroid use.
III. Treatment for moderate-to-severe disease not amenable to topicals includes systemic immunosuppressants (e.g., corticosteroids, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil) and dupilumab (Dupixent), a biologic IgG4 that is FDA-approved for pediatrics and adults as a biologic option for moderate-to-severe AD. Currently, there are no head to head trials evaluating safety and/or efficacy differences or superiority between tralokinumab (Adbry) and other therapies. Dupilumab (Dupixent) has an established safety and efficacy profile for the treatment of atopic dermatitis and is approved down to six years of age.

IV. There may be patient specific scenarios in which the use of additional topical agents following failure of one class of topical agents would be impractical. Insight from dermatology specialists indicate that patients who have at least 15% BSA involvement, or involvement in sensitive areas (e.g., eyelids, axilla, genitals, gluteal cleft), and have severe disease are potential candidates for systemic biologic therapy. Severe disease, as defined by NICE guidelines, includes widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking, and alteration of pigmentation), and severe limitation of everyday activities and psychosocial functioning, nightly loss of sleep; severe disease can also be classified as physician's global assessment (PGA) score of 4.0. Additionally, administration of topical agents may become impractical for patients with high disease burden (BSA ≥ 20%), considering twice daily administration is necessary for non-steroid topical agents for optimal efficacy.

V. Tralokinumab (Adbry) was evaluated in three randomized, double-blind, placebo-controlled, Phase III trials. Two as monotherapy (ECZTRA 1 and ECZTRA 2) and one in addition to topical corticosteroids (ECZTRA 3). Medication was administered as a 600 mg loading dose on day 0, followed by 300 mg every two weeks or placebo. In ECZTRA 1 and 2: at 16 weeks, responders continued on and were re-randomized to continue 300 mg every two weeks, change to 300 mg every four weeks, or placebo. In ECZTRA 3: at 16 weeks responders were re-randomized to tralokinumab (Adbry) every two or four weeks. All patients included in the trials were adults, and safety and efficacy in adolescent and pediatric patients is unknown. Patients included in the trials had moderate-to-severe AD (IGA 3-4) with BSA of at least 10% and had insufficient response to topical therapies. The majority had utilized several topical therapies, systemic immunosuppressants and phototherapy. Patients in ECZTRA 3 (6%) had history of use of dupilumab (Dupixent), and patients in ECZTRA 1 and 2 did not have a history of use.

VI. Tralokinumab (Adbry) showed positive outcomes in all three trials with regard to morbidity, symptom control, and quality of life parameters via proportion of patients with an IGA of 0 or 1, proportion of patients meeting EASI 75, SCORAD change, change in NRS score from baseline, DLQI, and in ECZTRA 3 – TCS utilization - further details on measurement tools are provided in the appendix below.

VII. ECZTRA 1 and 2: When responders of therapy were re-randomized to tralokinumab (Adbry) every two weeks, every four weeks, or placebo, the majority of patients on every two-week therapy maintained response, while there was a nonsignificant difference in response maintained between the every-two-week and placebo arms for maintenance in ECZTRA 1. This was attributed to patients being counted as non responders if any other therapy (e.g., TCS) was utilized. Additionally, many of those that were transitioned to placebo maintained response out to week 52. There was a difference seen in maintenance of response in ECZTRA 2 vs. placebo.

VIII. ECZTRA 3: Those that did not achieve the endpoints at week 16 were allowed to continue therapy, of those patients, 30.5% met IGA 0/1 and 55.8% met EASI 75 at week 32. Additionally, after re-randomization to tralokinumab (Adbry) every two weeks or every four weeks, 90% and 78% of patients maintained IGA 0/1, respectively, and 92.2% and 90.8% of patients maintained EASI 75, respectively.

IX. The overall incidence of adverse events (AE) was similar to placebo in clinical trials. Common AE (>5%): AD, URTI, skin infection, pruritus, headache, and conjunctivitis. Eye disorders are notable AE for tralokinumab (Adbry) as there was more URI (up to 3% greater) and conjunctivitis (up to

5% greater) seen in tralokinumab (Adbry) then in placebo. In addition, there were also eight cases of keratoconjunctivitis and keratitis compared to the one case seen on placebo. These AE's are seen similarly for dupilumab (Dupixent). Skin infections overall, as well as those that required systemic treatment, were greater in the placebo group. A long-term extension trial evaluating safety (EZTEND) is expected to be complete in September 2021.

X. There is lack of head-to-head clinical trial data for the AD FDA-approved therapies, and superior safety and efficacy of any product cannot be confidently concluded. Thus, it is reasonable that, pending no contraindication to therapy, preferred therapies be based on cost-effectiveness.

Investigational or Not Medically Necessary Uses

I. Tralokinumab (Adbry) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Asthma or COPD
   B. Nasal polyps
   C. Pediatric or adolescent atopic dermatitis
   D. Ulcerative colitis
   E. Alopecia areata

Appendix

Outcomes Key		
Name	**Explanation**	**Use and Significance**
IGA: Investigators Global Assessment Scale	Five-point scale assesses AD severity: 0-4, 0 is clear and 4 is severe. Decrease in score indicates improvement of AD signs and symptoms.	-Used for clinical trials -Clinically important difference is a 1-point change
EASI: Eczema Area and Severity Index	Scale assesses severity and extent of AD, 0-72 points. EASI 75 = 75% improvement from baseline. Measures 4 characteristics: erythema, infiltration/papulation, excoriations, lichentification, each on a scale of 0-3. These have different weight for each of the four body regions and are summed.	-Used for clinical trials -Clinically important difference is a 7-point change
SCORAD: Scoring Atopic Dermatitis	Tool used to evaluate severity and extent of AD. Assesses 3 components: BSA, severity, and symptoms. Extent is assessed as a percentage of each defined body area and reported as a sum. Maximum score is 100% for extent. The severity of six symptoms is assessed using a four-point scale: erythema, swelling, oozing/crusting, excoriation, skin thickening/lichentification, dryness. Severity has a maximum score of 18 points. Symptoms are recorded on a scale of 0-10, where 10 is the worst score imaginable. Entire score has a maximum of 103, higher scores=more severe condition.	-Used in clinical trials -Clinically important difference is a ~9 point change.
NRS: Pruritus Numerical Rating Scale	Tool used by patients to report the intensity of their itch. A scale of 0-10: 10 being worst itch imaginable. Often measured as a weekly average of the peak daily pruritus, tracked throughout a trial.	-Used in clinical trials -Clinically importance difference is 3-4 points.
DLQI: Dermatology Life Quality Index	Tool used widely in dermatology. 10 item questionnaire, assesses 6 aspects: feelings, activities, leisure, work/ school performance, personal relationships, treatment. Max score per question is 3. DLQI is calculated by summing of scores for a maximum of 30. 0-1: no effect, 21-30: extremely large effect.	-Sometimes used in practice. -Clinically important difference is 2-7-point change.

References

1. Wollenberg A., Blauvelt A., Guttman-Yassky E., et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicenter, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). Br J Dermatol. 2020 Sep 30. doi: 10.1111/bjd.19574. Epub ahead of print. PMID: 33000465.
2. Silverberg JI, Toth D, Bieber T, Alexis AF. Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: results from the double-blind, randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial. Br J Dermatol. 2020 Sep 30. doi: 10.1111/bjd.19573. Epub ahead of print. PMID: 33000503.
3. American Academy of Dermatology – Guidelines of Care for the Management of Atopic Dermatitis (2014). Available at: https://www.aad.org/member/clinical-quality/guidelines/atopic-dermatitis
4. Eichenfield L., Tom, W., Chamlin S., et al. Guidelines of care for the management of atopic dermatitis. JAAD. 2014 Feb 1. 70(2): 338-351.
5. Clinical Review Report: Dupilumab (Dupixent): (Sanofi-Aventis Canada Inc.): Indication: Moderate-to-severe atopic dermatitis (AD) [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2018 Jul. Appendix 5, Validity of Outcomes Measures. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539234/
6. Dupixent [Prescribing Information]. Regeneron Sanofi Genzyme. Tarrytown, NF. January 2021.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated criteria to include age expansion to 12 years and older based on FDA approval; updated supportive evidence.	03/2024
Review conducted. Update to supporting evidence	02/2023
Effective 01/01/2023 – Update to require trial of, or contraindication to, Dupixent and Rinvoq	12/2022
Added requirement that Adbry will not be used in combination with other biologic or non-biologic specialty medications to initial criteria	10/2022
Policy created	02/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP100

Description

Trametinib (Mekinist) is an orally administered mitogen-activated extracellular signal which regulates kinase 1 (MEK1) and MEK2 activation and MEK1 and MEK2 activity, while also inhibiting BRAF V600 mutation-positive melanoma cell growth. Dabrafenib (Tafinlar) is an orally administered BRAF V600 inhibitor. When used in combination, there is greater and prolonged inhibition compared to either drug alone.

Length of Authorization

- Initial: Six months
- Renewal:
  i. Six months for adjuvant treatment of melanoma that had lymph node involvement and was completely resected. One time renewal only (i.e., one total year of therapy authorized).
  ii. 12 months for all other indications

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
trametinib (Mekinist)	Anaplastic thyroid carcinoma, advanced or metastatic, BRAF V600E mutated, combination therapy Melanoma, adjuvant therapy for malignant disease, BRAF V600E or K mutated, combination therapy Melanoma, malignant unresectable or metastatic disease, BRAF V600E or K mutated, combination therapy Melanoma, malignant unresectable or metastatic disease, BRAF V600E or K mutated, monotherapy in BRAF treatment naïve patients Non-small cell lung cancer, metastatic, BRAF V600E mutated, combination therapy Unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options Pediatric low-grade glioma (LGG) with a BRAF V600E mutation, combination therapy	0.5 mg tablet	90 tablets/30 days
		2 mg tablet	30 tablets/30 days
		0.05 mg/mL solution	1,200 mL/30 days
dabrafenib (Tafinlar)		50 mg capsule	120 capsules/30 days
		75 mg capsule	
		10 mg soluble tablet	360 tablets/30 days

Initial Evaluation

I. **Trametinib (Mekinist) and dabrafenib (Tafinlar)** may be considered medically necessary in combination when the following criteria below are met:
   A. The medication is prescribed by, or in consultation with, an oncologist; **AND**
   B. The prescriber attests trametinib (Mekinist) and dabrafenib (Tafinlar) will be used in combination AND no other oncolytic medication will be used concurrently; **AND**
   C. The member has not previously progressed on any prior BRAF-inhibitor therapy (e.g., vemurafenib); **AND**
   D. A diagnosis of one of the following:
      1. **Anaplastic thyroid carcinoma**; **AND**
         i. The member is 18 years of age or older; **AND**
         ii. The disease has been tested and shown to have BRAF V600E mutation; **AND**
            a. The disease is metastatic (stage IV); **OR**
            b. The disease is locally advanced (stage IVA or IVB); **AND**
               i. The member has received standard of care for the condition (e.g., surgery, radiation therapy, chemotherapy); **OR**
               ii. There are no satisfactory locoregional treatment options; **OR**
      2. **Melanoma**; **AND**
         i. The member is 18 years of age or older; **AND**
         ii. The disease has been tested and shown to have BRAF V600E or V600K mutation; **AND**
         iii. Melanoma is advanced (stage III), metastatic (stage IV), or unresectable; **OR**
            a. Melanoma has lymph node involvement and will be used as adjuvant treatment after complete resection; **OR**
      3. Non-small cell lung cancer; AND
         i. The member is 18 years of age or older; **AND**
         ii. The disease has been tested and shown to have V600E mutation.
      4. Pediatric low-grade glioma (LGG); AND
         i. The member is between the ages of 1 and 17 years; **AND**
         ii. The disease has been tested and shown to have V600E mutation; **AND**
         iii. Disease has progressed following surgical excision; **OR**
            a. Attestation the member is not a candidate for surgical intervention; **AND**
         iv. Attestation the member has not undergone prior systemic or radiotherapy

II. Trametinib (Mekinist) and dabrafenib (Tafinlar) are considered not medically necessary when criteria above are not met and/or when used for:
   A. Treatment after prior BRAF inhibitor therapy

III. Trametinib (Mekinist) and dabrafenib (Tafinlar) are considered investigational when used for all other conditions, including but not limited to:
   A. Erdheim Chester Disease
   B. Leukemias, lymphomas
   C. Neurofibromatosis type 1 (NF1)
   D. BRAF V600E mutated unresectable or metastatic solid tumors
   E. Pediatric Low-Grade Glioma, second line systemic therapy

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. The prescriber attests trametinib (Mekinist) and dabrafenib (Tafinlar) will be used in combination AND no other oncolytic medication will be used concurrently; **AND**
IV. Documentation is provided indicating disease response to therapy, as defined by stabilization of disease or decrease in size of tumor or tumor spread.

Supporting Evidence

I. Dabrafenib (Tafinlar) plus trametinib (Mekinist) has been evaluated in several clinical trials in adults. Pharmacokinetic and pharmacodynamic parameters have been studied in pediatric patients 6 years of age and older for the treatment of BRAF V600E mutated unresectable or metastatic solid tumors. However, safety and efficacy in pediatrics has not been established.
II. Given the specialized, high-touch care, nuances of treatment, monitoring, and consideration for patient specific goals required for the treatment of BRAF mutated cancers, therapy choices should be directed by a specialist.
III. Per the respective FDA labels dabrafenib (Tafinlar) and trametinib (Mekinist) are indicated as single agents for the treatment of unresectable or metastatic melanoma with BRAF V600E mutations as detected by an FDA-approved test. However, efficacy data to support non-combination use of these products is low quality. Trametinib (Mekinist) did not show to have efficacy in a trial evaluating as second-line therapy after previous therapy with BRAF inhibitors.
IV. Use of BRAF inhibitors (e.g., vemurafenib [Zelboraf], encorafenib [Braftovi]) therapy after disease progression on dabrafenib (Tafinlar) and trametinib (Mekinist), or vice versa, has not yet been evaluated for safety and efficacy in quality clinical trials.

Treatment of Anaplastic Thyroid Carcinoma

V. A study of dabrafenib (Tafinlar) administered with trametinib (Mekinist) evaluated subjects with thyroid cancer that were BRAF V600E mutation positive. The open-label, single-arm trial included those that were locally advance, unresectable, or metastatic with no locoregional treatment options. Primary outcomes were ORR and DOR.

Treatment of Melanoma

VI. The METRIC study evaluated trametinib (Mekinist) as monotherapy in V600E or V600K mutation-positive, unresectable, or metastatic melanoma. It was an open-label trial against chemotherapy (dacarbazine or paclitaxel). The primary outcome was progression-free survival (PFS), and statistically favored trametinib (Mekinist).

VII. The COMBI-d study was a double-blind, active controlled trial of dabrafenib (Tafinlar) plus trametinib (Mekinist) versus dabrafenib (Mekinist) alone. Subjects included had unresectable or metastatic BRAF V600E or V600K mutation-positive cutaneous melanoma. Combination therapy was statistically favorable in PFS and overall-survival (OS).

VIII. The COMBI-AD trial evaluated dabrafenib (Tafinlar) with trametinib (Mekinist) versus placebo in those with stage III melanoma with BRAF V600E or V600K mutations. Results statistically favored dabrafenib (Tafinlar) plus trametinib (Mekinist) compared to placebo.

IX. Trametinib (Mekinist) was evaluated for efficacy in melanoma in those that had previously received BRAF inhibitor therapy. No patients achieved partial or complete response.

X. Dabrafenib (Tafinlar) was evaluated as monotherapy for BRAF V600E mutation positive unresectable or metastatic melanoma in the BREAK-3 study. The open-label trial evaluated dabrafenib (Tafinlar) versus dacarbazine, which demonstrated a statistically significant increase in PFS compared to dacarbazine.

XI. Dabrafenib (Tafinlar) was evaluated in the BREAK-MD study as a single-arm, Phase 2, open-label trial for mutation-positive melanoma, metastatic to the brain. The primary outcomes were ORR and DOR.

XII. The COMBI-d study evaluated dabrafenib (Tafinlar) to trametinib (Mekinist) plus dabrafenib (Tafinlar) in first-line therapy for unresectable or metastatic BRAF V600E or V600K mutation-positive cutaneous melanoma. Overall survival was statistically in favor of combination therapy.

XIII. The COMBI-v study evaluated dabrafenib (Tafinlar) plus trametinib (Mekinist) versus vemurafenib (Zelboraf) for BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma, and overall survival data was statistically in favor of dabrafenib (Tafinlar) plus trametinib (Mekinist).

XIV. Adjuvant therapy for melanoma that had lymph node involvement and was completely resected, therapy is authorized for a total of one year maximum. Safety and efficacy beyond this time frame has not been sufficiently established.

XV. Dabrafenib (Tafinlar) was evaluated as monotherapy for BRAF V600E mutation positive unresectable or metastatic melanoma in the BREAK-3 study. The open-label trial evaluated dabrafenib (Tafinlar) versus dacarbazine, which demonstrated a statistically significant increase in PFS compared to dacarbazine.

Treatment of NSCLC

XVI. A study of dabrafenib (Tafinlar) alone or administered with trametinib (Mekinist) was evaluated in an open-label, Phase 2 trial in subjects with BRAF V600E mutation-positive NSCLC. Combination therapy was statistically favored in overall response rate (ORR) and duration of response (DOR).

XVII. Insight from oncology specialists indicate that the diagnosis of stage IV metastatic disease can include intra-pulmonary (disease contained within the lungs) and extra-pulmonary (disease spread to organs outside the lungs) metastases. Intra-pulmonary metastases are typically staged as M1a and described as one of the following situations: separate nodule in the other lung, pleural or pericardial nodules, or malignant pleural or pericardial effusions. The treatment

approach for those with intra-pulmonary metastases should be individualized and include surgery and, when surgery is not feasible, standard systemic therapy.

Treatment of Pediatric Low-Grade Glioma

XVIII. In March of 2023 combination dabrafenib (Tafinlar) and trametinib (Mekinist) was FDA approved for pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy. Approval was based on results from the TADPOLE trial – a phase II/III open label trial comparing combination dabrafenib (Tafinlar)/trametinib (Mekinist) to standard of care carboplatin/vincristine.

XIX. Following the initial diagnostic work-up, surgery is the first treatment modality for almost 80% of all LGG patients. Where complete resection is possible and felt to be without great risk of morbidity then surgery should take place. Following surgery, follow-up and observation only, may be indicated.

XX. Trial participants included those aged 1 to 17 with BRAF V600 mutation- positive LGG whose tumor was unresectable and who required first line systemic therapy. Randomization was 2:1 with a majority of patients being female (60%) and white (72%). Patients treated with dabrafenib plus trametinib (n = 73) achieved an overall response rate (ORR) of 46.6% (95% CI, 34.8%-58.6%) compared with 10.8% (95% CI, 3.0%-25.4%) for patients treated with carboplatin plus vincristine (n = 37; P < 0.001). Patients in the dabrafenib/trametinib arm experienced a median duration of response of 23.7 months (95% CI, 14.5-not estimable [NE]); this was NE (95% CI, 6.6-NE) in the carboplatin/vincristine arm. Median progression free survival was reported as 20.1 (95% CI, 12.8-NE) and 7.4 (95% CI, 3.6-11.8) in the dabrafenib/trametinib arm and carboplatin/vincristine arms respectively with a hazard ratio of 0.31 (0.17-0.55). The OS results at interim analysis did not reach statistical significance. ORR is not a direct measure of drug benefit and is not an optimal surrogate marker or predictor of long-term efficacy, morbidity, or mortality.

Investigational or Not Medically Necessary Uses

I. Treatment after previous BRAF inhibitor therapy
   A. Trametinib (Mekinist) did not show to have efficacy in a trial evaluating as second-line therapy after previous therapy with BRAF inhibitors.

II. Safety and efficacy of trametinib (Mekinist) and/or dabrafenib (Tafinlar) has not been sufficiently evaluated for safety and/or efficacy in the following settings:
   A. Erdheim Chester Disease
      i. Only vemurafenib (Zelboraf) is FDA-approved for ECD with BRAF V600E mutation, though due to limited treatment options, other targeted therapies, such as trametinib (Mekinist) and dabrafenib (Tafinlar), are used off-label based on limited retrospective data.
   B. Leukemias, lymphomas
   C. Neurofibromatosis type 1 (NF1)
   D. Unresectable or metastatic solid tumors
      i. In May 2022, combination dabrafenib (Tafinlar) and trametinib (Mekinist) was approved via an accelerated approval pathway for the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid

BRAF V600E mutated tumors who have progressed following prior treatment and have no satisfactory alternative treatment options. Approval was based on results from three clinical trials, the Phase 2 ROAR (Rare Oncology Agnostic Research) basket study, Subprotocol H of the Phase 2 NCI-MATCH study, and Study X2101.

ii. Subprotocol H of the NCI-MATCH Trial was an open-label, single-arm study of 29 participants with BRAFV$^{600E/K/R/D}$ mutated solid tumors, lymphoma, or multiple myeloma whose disease had progressed on at least one standard therapy. The study combined multiple cancer types (16), most of which were represented as single cases. The primary outcome measure was objective response rate (ORR), which was observed in 37.9% of patients (90% CI, 22.9% to 54.9%; P< 0.001). Median progression free survival of 11.4 months and median duration of response of 21.1 months. Due to the study design, small sample size, and lack of endpoints correlated with validated clinical outcomes the applicability of this data for clinical decision making is limited.

iii. The Rare Oncology Agnostic Research (ROAR) basket trial was designed to assess the activity and safety of dabrafenib plus trametinib combination treatment in patients with BRAFV600E-mutated rare cancers. Interim results from the biliary tract cancer and low-grade glioma/high-grade glioma cohorts have been released. Primary endpoints for each of the studies was objective response rate (ORR). For the biliary tract cohort ORR was met by investigator-assessment [51% (95% CI 36-37); 22 of 43 patients] but not independent reviewer-assessment [47% (95% CI 31-62); 20 of 43 patients]. Median PFS was 9 months and median overall survival was 14 months. For the glioma cohorts, investigator assessed ORR was 33% in high-grade glioma (32% in glioblastoma) and 69% in low-grade glioma. Similar response rates were reported by independent radiology review (high-grade glioma 31%; low-grade glioma 69%). Investigator and independent reviewer reported duration of response and median PFS widely differed in the high-grade and low-grade cohorts which causes questionability for the true duration or response and PFS.

iv. Study X2101 was a four-part, phase I/IIa, multi-center, open label study in pediatric patients with refractory or recurrent tumors. Pharmacokinetic and pharmacodynamic parameters were reported. Additional study arms went on to trial combination treatment; however, only low-grade glioma (20 participants) and Langerhans cell histiocytosis (10 participants) were reported. Overall, this data gives general dosing information but does not necessarily give actionable clinical efficacy data when making clinical decisions in children.

E. Pediatric Low-Grade Glioma, second line systemic therapy

i. Clinical trials for the pediatric low grade glioma population included only those with BRAF V600–mutant low-grade glioma with progressive disease following surgical excision or non-surgical candidates who needed to begin first systemic treatment because of a risk of neurological impairment with progression. Trametinib (Mekinist) and dabrafenib (Tafinlar) combination therapy after the first line systemic therapy setting has not been evaluated.

Appendix

I. Table 1: Recommended Dosage for TAFINLAR Tablets for Oral Suspension (Weight-based)

Body weight	Recommended dosage
8 to 9 kg	20 mg twice daily
10 to 13 kg	30 mg twice daily
14 to 17 kg	40 mg twice daily
18 to 21 kg	50 mg twice daily
22 to 25 kg	60 mg twice daily
26 to 29 kg	70 mg twice daily
30 to 33 kg	80 mg twice daily
34 to 37 kg	90 mg twice daily
38 to 41 kg	100 mg twice daily
42 to 45 kg	110 mg twice daily
46 to 50 kg	130 mg twice daily
≥ 51 kg	150 mg twice daily

II. Table 2: Recommended Dosage for TAFINLAR Capsules in Pediatric Patients (Weight-based)

Body weight	Recommended dosage
26 to 37 kg	75 mg orally twice daily
38 to 50 kg	100 mg orally twice daily
51 kg or greater	150 mg orally twice daily

III. Table 3: Recommended Dosage for MEKINIST for Oral Solution (Weight-based)

Body weight	Recommended dosage total volume of oral solution once daily (trametinib content)
8 kg	6 mL (0.3 mg)
9 kg	7 mL (0.35 mg)
10 kg	7 mL (0.35 mg)
11 kg	8 mL (0.4 mg)
12 to 13 kg	9 mL (0.45 mg)
14 to 17 kg	11 mL (0.55 mg)
18 to 21 kg	14 mL (0.7 mg)
22 to 25 kg	17 mL (0.85 mg)
26 to 29 kg	18 mL (0.9 mg)
30 to 33 kg	20 mL (1 mg)
34 to 37 kg	23 mL (1.15 mg)
38 to 41 kg	25 mL (1.25 mg)
42 to 45 kg	28 mL (1.4 mg)
46 to 50 kg	32 mL (1.6 mg)
≥ 51 kg	40 mL (2 mg)

IV. Table 4: Recommended Dosage for MEKINIST Tablets in Pediatric Patients (Weight-based)

Body weight	Recommended dosage
26 to 37 kg	1 mg orally once daily
38 to 50 kg	1.5 mg orally once daily
51 kg or greater	2 mg orally once daily

References

1. Mekinist [Prescribing Information]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation. March, 2023.
2. Tafinlar [Prescribing Information]. Easy Hanover, New Jersey: Novartis Pharmaceuticals Corporation. March, 2023.
3. Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med. 2012;367(2):107-14.
4. Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet. 2015;386(9992):444-51.
5. Long GV, Hauschild A, Santinami M, et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. N Engl J Med. 2017;377(19):1813-1823.
6. Planchard D, Smit EF, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated BRAF-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. Lancet Oncol. 2017;18(10):1307-1316.
7. Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid Cancer. J Clin Oncol. 2018;36(1):7-13.
8. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012;380(9839):358-65.
9. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;13(11):1087-95.
10. Salama AKS, Li S, Macrae ER, et al. Dabrafenib and Trametinib in Patients With Tumors With BRAFV600E Mutations: Results of the NCI-MATCH Trial Subprotocol H. J Clin Oncol. 2020;38(33):3895-3904.
11. Wen PY, Stein A, van den Bent M, et al. Dabrafenib plus trametinib in patients with BRAFV600E-mutant low-grade and high-grade glioma (ROAR): a multicentre, open-label, single-arm, phase 2, basket trial. Lancet Oncol. 2022;23(1):53-64. doi:10.1016/S1470-2045(21)00578-7.
12. Subbiah V, Lassen U, Élez E, et al. Dabrafenib plus trametinib in patients with BRAFV600E-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial. Lancet Oncol. 2020;21(9):1234-1243. doi:10.1016/S1470-2045(20)30321-1
13. Novartis Pharmaceuticals. Study to Investigate Safety, Pharmacokinetic (PK), Pharmacodynamic (PD) and Clinical Activity of Trametinib in Subjects With Cancer or Plexiform Neurofibromas and Trametinib in Combination With Dabrafenib in Subjects With Cancers Harboring V600 Mutations. Clinicaltrials.gov. July 14, 2021. Accessed August 18, 2022. https://clinicaltrials.gov/ct2/show/results/NCT02124772
14. Children's Cancer and Leukaemia Group. Guidelines for the diagnosis and management of paediatric and adolescent Low-Grade Glioma. July 2020. Accessed July 10, 2023. LGG_Guidelines_July_2020.pdf (cclg.org.uk)
15. Novartis. Novartis Tafinlar + Mekinist approved by FDA for pediatric patients with BRAF V600E low-grade glioma, the most common pediatric brain cancer. Mar 17, 2023. Accessed July 10, 2023. Novartis Tafinlar + Mekinist approved by FDA for pediatric patients with BRAF V600E low-grade glioma, the most common pediatric brain cancer | Novartis

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy

Policy Name	Disease state
encorafenib (Braftovi) binimetinib (Mektovi)	Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therapy
cobimetinib (Cotellic)	Unresectable or metastatic melanoma with a BRAF V600E or V600K mutation
vemurafenib (Zelboraf)	Unresectable or metastatic melanoma with a BRAF V600E mutation
	Erdheim-Chester Disease with a BRAF V600E mutation
selumetinib (Koselugo)	Neurofibromatosis type 1 (NF1)

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated QL table to include solution and soluble tablet formulations. Added BRAF mutated pediatric LGG indication to the initial review section with supporting evidence. Added appendix dosing tables for pediatric dosage forms.	10/2023
Updated QL table, renewal criteria, and related policies to align with standard formatting. Divided supporting evidence per indication. Added NF1 and unresectable or metastatic solid tumors to E/I section. Removed specialist requirement upon renewal	10/2022
Added supporting evidence around stage IV metastatic disease and metastases.	10/2021
Criteria transitioned to policy, medications combined into one policy, addition of specialty prescriber, age edit, clarification on previous or alternative therapies to be considered for thyroid cancer. Quantity level limits updated.	11/2018
Criteria updated to include new indications of NSCLC and anaplastic thyroid cancer.	06/2018
Previous Reviews	11/2013
	01/2015

Policy Type: PA/SP Pharmacy Coverage Policy: UMP142

Description

Lonsurf combines trifluidine and tipiracil. Trifluidine is an orally administered nucleoside analog that is incorporated into DNA to interfere with DNA synthesis and proliferation; while, tipiracil increases exposure to trifluridine by inhibiting thymidine phosphorylase.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
trifluridine/tipiracil (Lonsurf)	Stomach or esophagogastric adenocarcinoma – metastatic, previously treated Colorectal cancer – metastatic, previously treated	15 mg/6.14 mg tablets	80 tablets/28 days
		20 mg/8.19 mg tablets	80 tablets/28 days

Initial Evaluation

I. **Trifluridine/tipiracil (Lonsurf)** may be considered medically necessary when the following criteria below are met:
   A. The member is 18 years of age or older; **AND**
   B. The medication is prescribed by, or in consultation with, an oncologist or a gastroenterologist; **AND**
   C. A diagnosis of one of the following:
      1. **Colorectal cancer**; **AND**
         i. The disease is metastatic (i.e., stage IV); **AND**
         ii. The member has been previously treated with a fluoropyrimidine (e.g., fluorouracil, capecitabine, S-1), oxaliplatin, and irinotecan-based chemotherapy; **AND**
         iii. The tumor has been tested and is documented to be KRAS mutant-type; **OR**
            a. The tumor has been tested and is documented to be KRAS wild-type; **AND**
               i. The member has been previously treated with an anti-EGFR therapy (e.g., cetuximab, panitumumab); **AND**
         iv. Trifluridine/tipiracil (Lonsurf) will be used as monotherapy; **OR**

a. Trifluridine/tipiracil (Lonsurf) will be used in combination with an anti-VEGF biological therapy (e.g., bevacizumab); **OR**

2. **Gastric or gastroesophageal junction adenocarcinoma**; **AND**
   i. The disease is metastatic (i.e., stage IV); **AND**
   ii. The member has received at least two prior lines of chemotherapy that have included a fluoropyrimidine (e.g., fluorouracil, capecitabine, S-1), a platinum therapy (e.g., cisplatin, carboplatin, oxaliplatin), and one of the following: a taxane (e.g., docetaxel, paclitaxel) or irinotecan; **AND**
   iii. The tumor is HER2- overexpression negative (HER2-negative); **OR**
      a. The tumor is HER2- overexpression positive (HER-2 positive); **AND**
         i. The member has received prior HER2/neu-targeted therapy (e.g., trastuzumab); **AND**
   iv. Provider attests that trifluridine/tipiracil (Lonsurf) is being requested as a third-line or subsequent therapy; **AND**
   v. Trifluridine/tipiracil (Lonsurf) will be used as monotherapy

II. Trifluridine/tipiracil (Lonsurf) is considered investigational when used for all other conditions, including but not limited to:
   A. Combination therapy with other oncolytic agents not outlined above
   B. Colorectal, gastric, or gastroesophageal cancer at a dose <20 mg/m2 orally twice daily
   C. Non adenocarcinoma gastric or gastroesophageal junction (e.g., squamous cell type)
   D. Gastric or gastroesophageal junction adenocarcinoma prior to at least two previous lines of chemotherapy and prior to use of all of the following: a fluoropyrimidine, a platinum therapy, and one of the following – taxane or irinotecan
   E. Biliary track cancers
   F. Tumors that are not colorectal, gastric or gastroesophageal in nature

Renewal Evaluation

I. Member has a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Documentation of member's current body surface area is provided in meters squared; **AND**
IV. Trifluridine/tipiracil (Lonsurf) is being used at or above a dose of 20 mg/m2; **AND**
V. The member has not experienced disease progression while on trifluridine/tipiracil (Lonsurf); **OR**
   - Documentation of compelling clinical evidence of benefit is provided if therapy is to be continued in the setting of progression.

Supporting Evidence

I. Trifluidine is an orally administered nucleoside analog that is incorporated into DNA to interfere with DNA synthesis and proliferation, and tipiracil increases exposure to trifluridine by inhibiting thymidine phosphorylase. The clinical trials for FDA-approval of trifluridine/tipiracil (Lonsurf) were in patients 18 years and older; therefore, there is a lack of safety and efficacy data from clinical trials for use in pediatric patients.

II. Many treatment options exist for the conditions listed in this policy. Initial and next line therapies in these settings is contingent upon patient specific characteristics. Given the complexities surrounding diagnosis and treatment choices, targeted drug therapies should be prescribed by, or in consultation with, a specialist.

III. Pivotal clinical trials for FDA-approved indications evaluated safety and efficacy of trifluridine/tipiracil (Lonsurf) as monotherapy in heavily pretreated patients. The therapies listed in the above criteria had been tried and failed by the majority of patients enrolled in the clinical trials.

IV. **Colorectal Cancer (CRC)**

- The safety of LONSURF was evaluated in RECOURSE, a randomized (2:1), double-blind, placebo-controlled trial in patients with previously treated metastatic colorectal cancer. Patients had received at least 2 prior regimens of standard chemotherapy and were refractory to, or failing, all of the following within three months: Fluoropyrimidine, irinotecan and oxaliplatin, anti-VEGF biologic therapy, anti-EGFR therapy (if *RAS* wild type). Eight hundred total patients were enrolled and received LONSURF 35 mg/m2/dose (n=533) or placebo (n=265) twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. The primary outcome was overall survival (OS) measured every 8 weeks until defined endpoint. Secondary outcome measures were progression-free survival (PRS) and percentage of patients with adverse events. The median OS improved from 5.3 months with placebo to 7.1 months with LONSURF, and the hazard ratio for death in the LONSURF group versus the placebo group was 0.68 (95% confidence interval [CI], 0.58 to 0.81; P<0.001).
- Currently, trifluridine/tipiracil (Lonsurf) is approved by the FDA for use in monotherapy in both metastatic gastric cancer and metastatic colorectal cancer, mCRC. The NCCN revised their opinion on this for the mCRC guidelines allowing therapy with bevacizumab in combination with trifluridine/tipiracil (Lonsurf) versus requiring failure of bevacizumab first or requiring trifluridine/tipiracil (Lonsurf) to be used as monotherapy. The panel had this decision from a review of the following information: A phase I single-arm, open label study (C-TASK FORCE) where all patients (n=25) enrolled were refractory/intolerant to fluoropyrimidine, irinotecan, oxaliplatin, anti-VEGF therapy, and anti-EGFR therapy (if wild-type *KRAS*). The endpoint was PFS at 16 weeks which was 42.9%. Based on this information, a Danish phase II trial was done with 93 mCRC patients comparing trifluridine/tipiracil (Lonsurf) with and without bevacizumab. After a median follow-up of 10 months, the median PFS (primary endpoint) was 2.6 months for trifluridine/tipiracil (Lonsurf) alone compared to 4.6 months in combination with bevacizumab (HR, 0.45; 95% CI, 0.29-0.72; P = .0015). A retrospective study of 57 patients with refractory mCRC showed similar results, with an improved median OS for trifluridine/tipiracil

(Lonsurf) with bevacizumab versus without (14.4 months vs. 4.5 months; P < .001). Based on this data, the panel added +/- use of bevacizumab as a treatment option for patients progressing through standard therapies. This same treatment is currently being evaluated in a phase III trial, SUNLIGHT, due for completion in 2023.

V. **Gastric or gastroesophageal junction adenocarcinoma**
    - The safety of LONSURF was evaluated in TAGS, an international, randomized (2:1), double blind, placebo-controlled trial in patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma who were previously treated with at least 2 prior chemotherapy regimens for advanced disease. Previous treatments must have included a fluoropyrimidine, a platinum, and either a taxane or irinotecan. Patients with HER2/neu-positive tumors must have received prior HER2/neu-targeted therapy, if available. Adjuvant chemotherapy could be counted as one prior regimen in patients who had recurrence during or within 6 months of completion of the adjuvant chemotherapy. Five hundred and seven total patients received either LONSURF 35 mg/m2 /dose (n=335) or placebo (n=168) twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle with best supportive care. The primary outcome was OS and secondary outcomes were PFS and adverse events. Median overall survival was 5.7 months (95% CI 4·8-6·2) in the trifluridine/tipiracil (Lonsurf) group and 3.6 months (3·1-4·1) in the placebo group (hazard ratio 0·69 [95% CI 0·56-0·85]; one-sided p=0·00029, two-sided p=0·00058). Presently, molecular testing for HER2 status, microsatellite instability status, and PD-L1 expression are used in the clinical management of locally advanced, unresectable, and metastatic EGJ cancers. HER2 testing is recommended for all patients with esophageal or EGJ cancer at the time of diagnosis if metastatic disease is documented or suspected.
    - There is no globally accepted standard for first-line treatment of HER2/neu negative gastric or gastroesophageal adenocarcinoma. When these indications were added to the policy, NCCN guidelines were not updated to provide recommendations for this agent. Clinical trial experience with extensive patient treatment history is the basis for addition into the policy.

VI. The recommended dosage for trifluridine/tipiracil (Lonsurf) is 35mg/m2/dose orally twice a day; however, due to the medication's adverse events, dose decreases are common and from the package insert, a maximum of 3 dose reductions are permitted. It is recommended to permanently discontinue trifluridine/tipiracil (Lonsurf) in patients who are unable to tolerate a dose of 20 mg/m2 orally twice daily and to not escalate dosage after it has been reduced. There is one exception to the 20mg/m2 and that is those with severe renal impairment (CrCl 15-29), who can go to 15mg/m2 and then should discontinue if unable to be tolerated.

Investigational or Not Medically Necessary Uses

All indications listed below have not been sufficiently studied for safety and efficacy, or have inconclusive evidence regarding safety and efficacy for use of trifluridine/tipiracil (Lonsurf).

I. Combination therapy with other oncolytic agents

II. Colorectal cancer prior to the metastatic setting, and/or prior to use of a fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy regimen, and/or prior to use of an anti-VEGF biological therapy, and/or if the member is KRAS mutant-type use prior to an anti-EGFR therapy
III. Colorectal, gastric, or gastroesophageal cancer at a dose < 20 mg/m2 orally twice daily
IV. Non adenocarcinoma gastric or gastroesophageal junction (e.g., squamous cell type)
V. Gastric or gastroesophageal junction adenocarcinoma prior to at least two previous lines of chemotherapy and prior to use of all of the following: a fluoropyrimidine, a platinum therapy, and one of the following – taxane or irinotecan
VI. Biliary track cancers
VII. Tumors that are not colorectal, gastric, or gastroesophageal in nature

References

1. Lonsurf [Prescribing Information]. Princeton, NJ. Taiho Oncology, Inc. Moda Health, Inc. Revised 12/2019.
2. Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2018;19(11):1437-1448.
3. Longo-muñoz F, Argiles G, Tabernero J, et al. Efficacy of trifluridine and tipiracil (TAS-102) versus placebo, with supportive care, in a randomized, controlled trial of patients with metastatic colorectal cancer from Spain: results of a subgroup analysis of the phase 3 RECOURSE trial. *Clin Transl Oncol*. 2017;19(2):227-235.
4. Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med*. 2015;372(20):1909-19.
5. Kuboki Y, Nishina T, Shinozaki E, et al. TAS-102 plus bevacizumab for patients with metastatic colorectal cancer refractory to standard therapies (C-TASK FORCE): an investigator-initiated, open-label, single-arm, multicentre, phase 1/2 study. Lancet Oncol. 2017 Sep;18(9):1172-1181. doi: 10.1016/S1470-2045(17)30425-4. Epub 2017 Jul 28.
6. UpToDate, Inc. Systemic therapy for locally advanced unresectable metastatic esophageal and gastric cancer. UpToDate, database online. Yoon H; Goldberg, R. Updated November 17. 2021. Accessed March 07, 2022. Available at: Progressive, locally advanced unresectable, and metastatic esophageal and gastric cancer: Approach to later lines of systemic therapy - UpToDate
7. UpToDate, Inc. Systemic chemotherapy for nonoperable metastatic colorectal cancer: treatment recommendations. UpToDate, database online. Clark J., Grothey A. Updated December 12, 2018. Accessed March 11, 2019. Available at: https://www.uptodate.com/contents/systemic-chemotherapy-for-nonoperable-metastatic-colorectal-cancer-treatment-recommendations?search=systemic%20chemotherapy%20for%20colorectal%20cancer&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
8. National Comprehensive Cancer Network. Esophageal and Esophagogastric Junction Cancer guideline Version 2.2022. Available at: gastric cancer (nccn.org) Accessed March 07, 2022.
9. National Comprehensive Cancer Network. Colon Cancer guideline Version1.2022. Available at: colon cancer (nccn.org). Accessed March 9, 2022.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
regorafenib (Stivarga)	Colorectal Cancer
encorafenib (Braftovi)	

Policy Implementation/Update:

Action and Summary of Changes	Date
Reformatted existing policy to match current standards. Updated renewal section to match requirements across other anti-cancer policies. Reviewed and updated references for building a better supportive evidence section. Included addition under mCRC for combination use with Avastin (bevacizumab). Updated initial approval duration from 3 months to 6 months.	10/2022
Added new indication of stomach and esophagogastric adenocarcinoma based on clinical trial data that demonstrated overall survival in the third line treatment setting.	03/2019
Policy originally created and effective	5/2015

Policy Type: PA/SP Pharmacy Coverage Policy: UMP210

Description

Triheptanoin (Dojolvi) is a medium-chain triglyceride oral solution that provides a source of calories and fatty acids to bypass the long-chain enzyme deficiencies.

Length of Authorization

- Initial: Four months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
triheptanoin (Dojolvi)	8.3kcal/mL oral solution	Fatty acid oxidation disorders (LC-FAOD)	Monthly quantity to allow for a maximum of 35% of prescribed daily caloric intake

Initial Evaluation

I. Triheptanoin (Dojolvi) may be considered medically necessary when the following criteria are met:
   A. Member is diagnosed with **molecularly confirmed LC-FAOD** by a specialist in genetic metabolic disorders; **AND**
   B. Member does not have pancreatic insufficiency; **AND**
   C. Member has a history of hypoglycemia or cardiomyopathy or at least one episode of rhabdomyolysis; **AND**
   D. Member has at least TWO of the following diagnostic criteria:
      1. One or more known gene mutations in: CPT2, ACADVL, HADHA, or HADHB; **OR**
      2. Disease specific elevation of acylcarnitines on a newborn blood spot or in plasma; **OR**
      3. Low enzyme activity in cultured fibroblasts; **AND**
   E. Documentation of prescribed daily caloric intake is provided; **AND**
   F. Provider attests that the member is utilizing dietary management (e.g. low fat, high carbohydrate diet, avoidance of fasting); **AND**
   G. Provider attests that treatment with over the counter MCT oil has been ineffective, contraindicated, or not tolerated.

II. Triheptanoin (Dojolvi) is considered investigational when used for all other conditions, including but not limited to:
   A. Pancreatic insufficiency

B. Fat malabsorption
C. Impaired chylomicron transport
D. Severe hyperchylomicronemia

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Prescriber attestation that the member has exhibited stability or improvement in disease activity [e.g., exercise tolerance, increased cardiac function tests]

Supporting Evidence

I. Per National Organization for Rare Disorders (NORD), disease state management of LC-FAOD is directed toward preventing and controlling acute episodes, which include symptoms such as hypoglycemia, rhabdomyolysis, and cardiac complications. Management often involves avoidance of fasting, maintaining low-fat, high-carbohydrate diet, and using low-fat nutritional supplements and MCT oil available over the counter (OTC).
II. Clinical presentation and the age of onset of LC-FAOD is variable. Signs and symptoms can be present at birth or develop later in adulthood. Even with treatment, many patients continue to experience symptom recurrence of variable frequency and severity. Hypoglycemia and cardiomyopathy typically occur at an earlier stage in life, rhabdomyolysis is usually present in asymptomatic patients later in adulthood. In addition to these three primary clinical manifestations, other symptoms are possible and include encephalopathy, peripheral neuropathy, and pigmentary retinopathy.
III. The effectiveness of triheptanoin (Dojolvi) has been established based on one phase 2, randomized, double-blind trial comparing triheptanoin (Dojolvi) with trioctanoin in 32 adult and pediatric patients (aged 7 years and older). Patients had a confirmed diagnosis of LC-FAOD, evidence of at least one significant episode of rhabdomyolysis, and at least two of the following diagnostic criteria: disease specific elevation of acylcarnitines on a newborn blood spot or in plasma, low enzyme activity in cultured fibroblasts, or one or more known pathogenic mutations in CPT2, ACADVL, HADHA, HADHB.
IV. The primary efficacy outcomes included changes in total energy expenditure (TEE), cardiac function by echocardiogram, exercise tolerance, and phosphocreatine recovery following acute exercise. Statistically significant outcomes were positive changes in left ventricular function and maximal heart rate reduction during an exercise tolerance test in the triheptanoin (Dojolvi) arm versus the trioctanoate arm.
V. The quality of the evidence was considered low because the study had a small sample size and had incomplete blinding. Moreover, there were applicability issues as some primary endpoints (cardiac function and exercise tolerance) were not clinically significant.
VI. Triheptanoin (Dojolvi) has not been directly compared to OTC MCT oil; therefore, there is insufficient evidence to conclude that triheptanoin (Dojolvi) is safer or more effective than OTC MCT oil.

VII. The most commonly reported adverse reactions for triheptanoin (Dojolvi) include gastrointestinal upset, musculoskeletal pain, fatigue, and headache.

VIII. There are no specific contraindications to using triheptanoin (Dojolvi), however, warnings include not using triheptanoin (Dojolvi) with feeding tubes manufactured of polyvinyl chloride (PVC) and avoiding use in patients with pancreatic insufficiency.

IX. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for using triheptanoin (Dojolvi) for indications other than LC-FAOD.

Investigational or Not Medically Necessary Uses

I. Triheptanoin (Dojolvi) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Pancreatic insufficiency
   B. Fat malabsorption
   C. Impaired chylomicron transport
   D. Severe hyperchylomicronemia

Appendix

The recommended target daily dosage of triheptanoin (Dojolvi) is up to 35% of the patient's total prescribed daily caloric intake (DCI) divided into at least four doses and administered with mealtimes or with snacks.

I. Table 1: Dosage initiation and titration

For patients not currently taking MCT product	• Initiate at total daily dosage of 10% DCI divided into four times per day. • Increase recommended daily dose of up to 35% DCI over a period of two to three weeks.
For patients switching from another MCT product	• Discontinue use of MCT products before starting triheptanoin (Dojolvi). • Initiate triheptanoin (Dojolvi) at the last tolerated daily dose of MCT divided into four times per day. • Increase the total daily dose by approximately 5% DCI every two to three days until target dose of up to 35% DCI is achieved.

II. The quantity limit is to be determined based on the member's prescribed daily caloric intake (DCI). Maximum total daily dose may not exceed 35% DCI. Round the total daily dosage to the nearest whole number.

$$\textit{Total Daily Dose (mL)} = \frac{\textit{Member's DCI (kcal) x Target (\% dose of DCI)}}{\textit{8.3 kcal/ml}}$$

References

1. Dojolvi [Prescribing Information]. Ultragenyx Pharmaceutical: Novato, CA. June 2020.
2. Gillingham MB, Heitner SB, Martin J, et al. Triheptanoin versus trioctanoin for long-chain fatty acid oxidation disorders: a double blinded, randomized controlled trial. J Inherit Metab Dis. 2017;40(6):831-843. doi:10.1007/s10545-017-0085-8
3. NORD (National Organization for Rare Disorders): Very Long Chain Acyl CoA Dehydrogenase Deficiency (LCAD). 2020. Available at: https://rarediseases.org/rare-diseases/very-long-chain-acyl-coa-dehydrogenase-deficiency-lcad/
4. Ultragenyx Pharmaceutical Inc., DOJOLVI (triheptanoin) for the Treatment of Long-chain Fatty Acid Oxidation Disorder. Dossier, version 1.0. June 30, 2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP281

Description

Trofinetide (Daybue) is an insulin-like growth factor-1 (IGF-1) analogue, FDA-approved for the treatment of Rett syndrome (RTT) in adults and children 2 years of age and older. Trofinetide (Daybue) is administered orally or via a gastrostomy tube twice daily according to weight-based dosing.

Length of Authorization

- Initial: three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
trofinetide (Daybue)	Rett syndrome (RTT)	200 mg/mL solution	*Weight based (see appendix table)*

Initial Evaluation

I. **Trofinetide (Daybue)** may be considered medically necessary when the following criteria are met:
   A. Member is 2 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with a provider experienced in the diagnosis and management of Rett syndrome (e.g., pediatrician, neurologist, geneticist); **AND**
   C. Documentation of member's weight within the last 3 months; **AND**
   D. Member has a diagnosis of **classic or typical Rett syndrome**; **AND**
      1. Diagnosis is confirmed by genetic testing that documents a mutation in *MECP2* gene; **AND**
      2. Provider attestation diagnosis is confirmed by ALL of the following clinical features of classic or typical RTT:
         i. Absence of grossly abnormal psychomotor development in first 6 months of life**; AND**
         ii. A period of regression followed by recovery or stabilization**; AND**
         iii. Partial or complete loss of acquired purposeful hand skills**; AND**
         iv. Partial or complete loss of acquired spoken language**; AND**
         v. Gait abnormalities: Impaired (dyspraxic) or absence of ability**; AND**
         vi. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms**; AND**
         vii. Absence of brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems

II. Trofinetide (Daybue) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:

A. Pediatric patients less than 2 years of age
B. Atypical or variant Rett syndrome (e.g., preserved speech (Zappella) variant, early onset seizures (Hanefeld) variant, and congenital (Rolando) variant)
C. *MECP2*-mutation related disorders without clinical diagnostic symptoms of classic/typical Rett syndrome (e.g., *MECP2*-related severe neonatal encephalopathy, *PPMX*-syndrome, *MECP2* duplication syndrome)
D. Other neurogenerative disorders or disorders that may have symptoms or physical features that are similar to Rett syndrome (e.g., autism spectrum disorder, encephalitis, spastic ataxia, cerebral palsy, spinocerebellar degeneration, leukodystrophies, neuroaxonal dystrophy)
E. *CDKL5*-mutation disorders (e.g., infantile spasms, West syndrome, Lennox-Gastaut syndrome)
F. Other metabolic or degenerative disorders (e.g., neuronal ceroid lipofuscinosis, phenylketonuria, and urea cycle disorders)
G. *FOXG1*-mutation related disorders
H. Pitt-Hopkins syndrome
I. Angelman syndrome

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Documentation of member's weight within the last 3 months; **AND**
IV. Provider attestation that trofinetide (Daybue) continues to slow or stabilize the progression of disease and treatment provides clinical benefit to the member.

Supporting Evidence

I. Rett syndrome (RTT) is a progressive X-linked neurodevelopmental disorder that almost exclusively affects females. In the United States, approximately 11,000 patients are affected by RTT. Infants with RTT generally develop normally for about 6 to 18 months after birth, at which point regression of early milestones occurs. The ability to communicate, walk, and eat halt and begin to regress. Gradual deterioration continues into and throughout adulthood. Patients with RTT have a reduced life expectancy into the forties or fifties.
II. Common features associated with progression of the disorder include severe loss of language skills, fine and gross motor skills, dysphagia, seizures, breathing abnormalities, growth failure, bone mineral deficits (including fractures), autonomic nervous system dysfunction, cardiac abnormalities, and tone abnormalities (dystonia and tremor).
III. Diagnostic criteria for RTT is based on specific clinical criteria to reflect the main disease features. The clinical presentation associated with typical RTT is defined by a regression of purposeful hand use and spoken language, with the development of gait abnormalities and

hand stereotypies. After the period of regression, a stage of stabilization and possibly improvement ensues, with some individuals partially regaining skills. Patients with atypical or variant RTT present with many of the clinical features of typical RTT, such as regression, but do not necessarily have all of the clinical features of typical RTT. There at three known forms of atypical RTT, including but not limited to the preserved speech (Zappella) variant, early onset seizures (Hanefeld) variant, and congenital (Rolando) variant RTT. Additional information about the diagnostic criteria are included in the appendix.

IV. Approximately 90-95% of RTT cases are caused by identifiable mutations of the *MECP2* gene. In 99% of cases, these mutations occur sporadically and are not possessed or transmitted by a child's parents (de novo mutations). Therefore, the vast majority of cases of RTT are not an inherited disorder. Mutations in *MECP2* have also been identified in individuals who do not have the clinical features of RTT, usually a history of regression, and therefore cannot be given a diagnosis of RTT. These clinical phenotypes emphasize that mutations in *MECP2* are not synonymous with RTT and that a mutation in *MECP2* is not sufficient to make the diagnosis of RTT. The diagnosis of RTT is made clinically as *MECP2* mutations are neither necessary nor sufficient to make the diagnosis of RTT.

V. Trofinetide (Daybue) is the first and only treatment FDA-approved to treat RTT. Treatments focus on managing symptoms and preventing complications. In addition to medications to help control specific symptoms, several non-drug approaches may be used to help manage the condition and improve patients' quality of life. All the treatments currently used are solely for management of the numerous complications of the disorder. These treatments include medications for epilepsy, constipation, and other systemic features, therapies to compensate for neurological impairment, and surgical therapies for dysphagia, contracture, and scoliosis are common. Functional abilities can be improved by various interventions such as physiotherapy, occupational therapy, hydrotherapy, and speech therapy. Given the complexity of the disease, diagnosis by a specialist or provider has consulted with a specialist in the area of the patient's diagnosis, such as a neurologist, pediatrician, or geneticist, is required.

VI. Trofinetide (Daybue) is a synthetic version of a naturally occurring molecule known as glycine-proline-glutamate (GPE), the N-terminal tripeptide of insulin-like growth factor. The mechanism by which trofinetide (Daybue) exerts therapeutic effects in patients with Rett Syndrome (RTT) is unknown. In animal studies, trofinetide has been shown to increase branching of dendrites and synaptic plasticity signals.

VII. The efficacy and safety of trofinetide (Daybue) were evaluated in the Phase 3 LAVENDER study, a 12-week, double-blind, randomized, placebo-controlled study that enrolled 187 female participants 5–20 years of age with RTT. Participants had a diagnosis of typical Rett syndrome according to the Rett Syndrome Diagnostic Criteria with a documented disease-causing mutation in the *MECP2* gene. Participants were randomized to receive trofinetide or matching placebo for 12 weeks. The trofinetide dosage was based on patient weight to achieve similar exposure in all patients. The co-primary endpoints included the Rett Syndrome Behavior Questionnaire (RSBQ) and Clinical Global Impression–Improvement (CGI-I) assessment.

    a. The RSBQ is a 45-item rating scale completed by the caregiver that assesses core symptoms of Rett syndrome (breathing, hand movements or stereotypies, repetitive behaviors, night time behaviors, vocalizations, facial expressions, eye gaze, and mood). Each item is scored as 0 (not true), 1 (somewhat or sometimes true), or 2 (very true or

often true), with a maximum possible score of 90 points. Lower scores reflect lesser severity in signs and symptoms of RTT.

i. The mean baseline RSBQ score was 43.7 for the DAYBUE group and 44.5 for the placebo group.

b. The CGI-I is rated by clinicians to assess whether a patient has improved or worsened on a 7-point scale (1=very much improved to 7=very much worse) in which a lower score indicates improvement.

i. Baseline CGI-I score was 4.9 in both groups.

VIII. Trofinetide (Daybue) demonstrated a statistically significant improvement over placebo in both co-primary endpoints. The RSBQ score change in trofinetide (Daybue) group was -4.9 compared to -1.7 change in placebo group was at week 12 (-3.2; 95% CI (-5.7, -0.6), p=0.018). The CGI-I score was 3.5 in the treatment group compared to 3.8 in the placebo group at week 12 (-0.3; 95% CI (-0.5- -0.1); p=0.003). A post-hoc analysis of CGI-I scores was conducted, which revealed that 61% of patients in the trofinetide (Daybue) had no change in RTT symptoms, while 25% had minimal improvement and 13% were much improved. In the placebo group, 81 % of patients had no change, 11% were minimally improved, and 5% were much improved.

IX. The common adverse events were diarrhea (81% with trofinetide vs 19% with placebo) and vomiting (27% with trofinetide vs 10% with placebo). About 12% of trofinetide-treated subjects compared to 4% of placebo-treated subjects experienced weight loss of greater than 7% of body weight. Although a majority (>95%) of adverse events were rated as mild to moderate, the label warnings and precautions include diarrhea and weight loss to ensure prescribers and patients are aware of these adverse reactions. Treatment was discontinued in 17% individuals in the trofinetide group compared to 2% in the placebo group due to treatment related adverse events, with diarrhea (15%) as the most common adverse reaction leading to discontinuation. Due to the frequency of diarrhea, concomitant therapy with loperamide was initiated in over 50% of subjects in the LAVENDER trial.

X. Although the LAVENDER trial enrolled patients age 5-20 years of age, trofinetide (Daybue) is FDA approved for the treatment of RTT in adults and pediatric patients 2 years of age and older. Efficacy in pediatric patients with RTT aged 2 to 4 years old was provided by an open-label PK study in which 13 patients completed 12 weeks of treatment with trofinetide (Daybue). Exposure and adverse reactions in pediatric patients 2 to 4 years of age treated with trofinetide (Daybue) were similar to those reported in adult and pediatric patients 5 years of age and older in the LAVENDER study.

XI. The inclusion criteria in the LAVENDER study enrolled all female participants, required all participants to have a diagnosis of classic or typical RTT (per diagnostic criteria from Neul et al. 2010), and confirmed *MECP2* mutation. The study excluded patients with atypical RTT, patients without a documented *MECP2* mutation, and male subjects to reduce variability and allow for a more homogeneous study population. Coverage of trofinetide (Daybue) will be considered for individuals with a confirmed clinical diagnosis of typical RTT and presence of *MECP2* mutation to mirror the study population. As of July 2023, efficacy and safety of trofinetide (Daybue) in patients with atypical RTT is unknown.

XII. The available evidence demonstrates statistically significant improvements in the primary endpoints studied, RSBQ and CGI-I, when trofinetide (Daybue) was compared to placebo. There is low to moderate confidence that trofinetide (Daybue) provides clinically meaningful symptom

relief or affects physical functioning due to lack of established minimal clinically important differences in the RSBQ and CGI-I scoring instruments. Additionally, the scoring instruments used as primary outcomes are subjective in nature and introduce assessment bias concerns. The impact of trofinetide (Daybue) on morbidity, mortality, or health-related quality of life among patients with RTT is also unknown. The impact of trofinetide (Daybue) on disease activity over time is unknown, however long-term data is currently being assessed in two Phase 3 open-label extension trials (LILAC-1, LILAC-2).

Investigational or Not Medically Necessary Uses

I. Trofinetide (Daybue) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Pediatric patients less than 2 years of age
   B. Atypical or variant Rett syndrome (e.g., preserved speech (Zappella) variant, early onset seizures (Hanefeld) variant, and congenital (Rolando) variant)
   C. *MECP2*-mutation related disorders without clinical diagnostic symptoms of classic/typical Rett syndrome (e.g., *MECP2*-related severe neonatal encephalopathy, *PPMX*-syndrome, *MECP2* duplication syndrome)
   D. Other neurogenerative disorders or disorders that may have symptoms or physical features that are similar to Rett syndrome (e.g., autism spectrum disorder, encephalitis, spastic ataxia, cerebral palsy, spinocerebellar degeneration, leukodystrophies, neuroaxonal dystrophy)
   E. *CDKL5*-mutation disorders (e.g., infantile spasms, West syndrome, Lennox-Gastaut syndrome)
   F. Other metabolic or degenerative disorders (e.g., neuronal ceroid lipofuscinosis, phenylketonuria, and urea cycle disorders)
   G. *FOXG1*-mutation related disorders
   H. Pitt-Hopkins syndrome
   I. Angelman syndrome

Appendix

I. Table 1: Quantity Limit/Dosing
   A. Available dosage form: Trofinetide 200mg/mL oral solution is available as a 450mL strawberry flavored oral solution in 500mL bottle
   B. Per the label, any unused trofinetide (Daybue) should be discarded after 14 days of first opening the bottle
   C. The dose prescribed is appropriate based on the individual's weight:

Patient Weight	Trofinetide (Daybue) Dosing	Trofinetide (Daybue) Volume	mL/Day supply (DS)	# Bottles/Day supply (DS)
9kg to less than 12kg	5,000 mg twice daily	25mL twice daily	1,500mL/27 days	3 bottles/27 days
12kg to less than 20kg	6,000 mg twice daily	30mL twice daily	2,000mL/30 days	4 bottles/30 days
20kg to less than 35kg	8,000 mg twice daily	40mL twice daily	2,500mL/28 days	5 bottles/28 days
35kg to less than 50kg	10,000 mg twice daily	50mL twice daily	3,000mL/28 days	6 bottles/28 days
50kg or more	12,000 mg twice daily	60mL twice daily	4,000mL/30 days	8 bottles/30 days

II. Table 2. Rett Syndrome Diagnostic Criteria (Source: Neul et al. 2010)

Required for typical or classic RTT
1. A period of regression followed by recovery or stabilization[*] 2. All main criteria and all exclusion criteria 3. Supportive criteria are not required, although often present in typical RTT
Main Criteria
1. Partial or complete loss of acquired purposeful hand skills. 2. Partial or complete loss of acquired spoken language[**] 3. Gait abnormalities: Impaired (dyspraxic) or absence of ability. 4. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms
Exclusion Criteria for typical RTT
1. Brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems[***] 2. Grossly abnormal psychomotor development in first 6 months of life[#]
Required for atypical or variant RTT
1. A period of regression followed by recovery or stabilization[*] 2. At least 2 out of the 4 main criteria 3. 5 out of 11 supportive criteria
Supportive Criteria for atypical RTT[##]
1. Breathing disturbances when awake 2. Bruxism when awake 3. Impaired sleep pattern 4. Abnormal muscle tone 5. Peripheral vasomotor disturbances 6. Scoliosis/kyphosis 7. Growth retardation 8. Small cold hands and feet 9. Inappropriate laughing/screaming spells 10. Diminished response to pain 11. Intense eye communication - “eye pointing”
[*]Because *MECP2* mutations are now identified in some individuals prior to any clear evidence of regression, the diagnosis of “possible” RTT should be given to those individuals under 3 years old who have not lost any skills but otherwise have clinical features suggestive of RTT. These individuals should be reassessed every 6–12 months for evidence of regression. If regression manifests, the diagnosis should then be changed to definite RTT. However, if the child does not show any evidence of regression by 5 years, the diagnosis of RTT should be questioned. [**]Loss of acquired language is based on best acquired spoken language skill, not strictly on the acquisition of distinct words or higher language skills. Thus, an individual who had learned to babble but then loses this ability is considered to have a loss of acquired language. [***]There should be clear evidence (neurological or ophthalmological examination and MRI/CT) that the presumed insult directly resulted in neurological dysfunction. [#]Grossly abnormal to the point that normal milestones (acquiring head control, swallowing, developing social smile) are not met. Mild generalized hypotonia or other previously reported subtle developmental alterations during the first six months of life is common in RTT and do not constitute an exclusionary criterion. [##]If an individual has or ever had a clinical feature listed it is counted as a supportive criterion. Many of these features have an age dependency, manifesting and becoming more predominant at certain ages. Therefore, the diagnosis of atypical RTT may be easier for older individuals than for younger. In the case of a younger individual (under 5 years old) who has a period of regression and ≥2 main criteria but does not fulfill the requirement of 5/11 supportive criteria, the diagnosis of “probably atypical RTT” may be given. Individuals who fall into this category should be reassessed as they age and the diagnosis revised accordingly.

References

1. Daybue. Package Insert. Acadia Pharmaceuticals Inc., San Diego, CA; March 2023.
2. The International Rett Syndrome Foundation. About Rett Syndrome. Accessed April 21, 2023. https://reverserett.org/about-rett-syndrome/

3. National Organization for Rare Disorders. Rett syndrome. Updated March 15, 2023. Accessed April 24, 2023. https://rarediseases.org/rare-diseases/rett-syndrome/#affected
4. Petriti U, et al. Global prevalence of Rett syndrome: systematic review and meta-analysis. Syst Rev. 2023;12(1):5. doi:10.1186/s13643-023-02169-6
5. Kozinetz CA, et al. Epidemiology of Rett syndrome: a population-based registry. Pediatrics. 1993;91(2):445-450. Accessed April 23, 2023. https://pubmed.ncbi.nlm.nih.gov/8424025/
6. Schultz R, et al. Rett syndrome: Genetic, clinical features, and diagnosis. Patterson MC, et al, eds. Waltham, MA: UptoDate Inc. Updated March 30, 2023. Accessed April 24, 2023. https://www.uptodate.com/contents/rett-syndrome-genetics-clinical-features-and-diagnosis
7. Fu C, et al. Consensus guidelines on managing Rett syndrome across the lifespan. BMJ Paediatr Open. 2020;4(1):e000717. doi:10.1136/bmjpo-2020-000717
8. Neul JL, Percy AK, Benke TA, et al. Design and outcome measures of LAVENDER, a phase 3 study of trofinetide for Rett syndrome. Contemp Clin Trials. 2022;114:106704. doi:10.1016/j.cct.2022.106704
9. Acadia Pharmaceuticals. Daybue (trofinetide) FDA approval call. Investor presentation. March 13, 2023. Accessed April 24, 2023. https://www.fda.gov/media/168491/download
10. Acadia Pharmaceuticals announces U.S. FDA approval of Daybue (trofinetide) for the treatment of Rett syndrome in adult and pediatric patients two years of age and older. News release. Acadia Pharmaceuticals; March 10, 2023. Accessed April 24, 2023. https://acadia.com/media/news-releases/acadia-pharmaceuticals-announces-u-s-fda-approval-of-daybue-trofinetide-for-the-treatment-of-rett-syndrome-in-adult-and-pediatric-patients-two-years-of-age-and-older/
11. Neul JL, Kaufmann WE, Glaze DG, et al. Rett syndrome: revised diagnostic criteria and nomenclature. Ann Neurol. 2010;68(6):944-950. doi:10.1002/ana.22124

Related Policies

Currently there are no related policies.

Policy Implementation/Update

Action and Summary of Changes	Date
Policy created	08/2023

Policy Type: PA/SP Pharmacy Coverage Policy: UMP194

Split Fill Management*

Description

Tucatinib (Tukysa) is an orally administered tyrosine kinase inhibitor that targets the growth of HER2-expressing tumors.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
tucatinib (Tukysa)	HER2- positive metastatic breast cancer	50 mg tablets	60 tablets/30 days
	HER2-positive RAS wild-type unresectable or metastatic colorectal cancer	150 mg tablets	120 tablets/30 days

Initial Evaluation

I. **Tucatinib (Tukysa)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. The member has **not** previously progressed on or after treatment with another tyrosine kinase inhibitor (e.g., lapatinib [Tykerb], neratinib [Nerlynx]); **AND**
   D. A diagnosis of **advanced or metastatic breast cancer** when the following are met:
      1. Documentation is provided showing the disease is HER2-positive; **AND**
      2. Will be used in combination with trastuzumab and capecitabine; **AND**
      3. Will not be used with any other oncology therapy outside of trastuzumab and capecitabine; **AND**
      4. Member does **not** have brain metastases; **AND**
         i. Member has progressed on, has a contraindicated to, or did not tolerate treatment with trastuzumab, pertuzumab, and trastuzumab emtansine (TDM-1); **OR**
      5. Member has brain metastases; **AND**
         i. Member has received ≥1 prior anti-HER2-based regimens in the metastatic setting

I. Tucatinib (Tukysa) is considered investigational when used for all other conditions, including but not limited to:
   A. Metastatic colorectal cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has experienced response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
IV. Tucatinib (Tukysa) will be used in combination with trastuzumab and capecitabine; **AND**
V. Tucatinib (Tukysa) will not be used with any other oncology therapy outside of trastuzumab and capecitabine

Supporting Evidence

I. Tucatinib (Tukysa) was studied in a phase 2, double blind, placebo controlled, randomized trial (HER2CLIMB) in 612 patients with HER2-positive metastatic breast cancer with, or without, brain metastases who had been previously treated with trastuzumab, pertuzumab, and trastuzumab emtansine (TDM-1). The trial evaluated treatment with tucatinib (Tukysa) in combination with trastuzumab and capecitabine versus placebo, trastuzumab, and capecitabine. Patients in the trial had a median of 4 previous lines of therapy and 48% of patients had brain metastases. Overall survival at 2 years was 44.9% with the tucatinib (Tukysa) combination and 26.6% with trastuzumab, capecitabine, and placebo combination (hazard ratio for death, 0.66; 95% CI, 0.50-0.88; P = 0.005). Median overall survival was 21.9 months (tucatinib (Tukysa) combination) and 17.4 months (placebo, trastuzumab, and capecitabine). Secondary outcome of progression free survival at 1 year in patients with brain metastases was 24.9% with the tucatinib (Tukysa) combination and 0% with trastuzumab, capecitabine, and placebo combination (hazard ratio, 0.48; 95% CI, 0.34-0.69; P < 0.001).
II. Patients in the HER2CLIMB trial were excluded if they were previously treated with neratinib, afatinib, or any HER2 tyrosine kinase inhibitor at any time previously. Those who were treated with lapatinib more than 12 months from the start of the study were allowed to enroll in the trial; however, this accounted for only 6% of patients in the HER2CLIMB trial. At this time, there is lack of scientific evaluation for safety and efficacy of tucatinib (Tukysa) following progression on or after another tyrosine kinase inhibitor.
III. Although patients in the trial were heavily pretreated having failed trastuzumab, pertuzumab, and trastuzumab emtansine (TDM-1), FDA approval was granted in adults with or without brain metastases who have received ≥1 prior anti-HER2-based regimens in the metastatic setting. Agents such as TDM-1 and other oral tyrosine kinase inhibitors (i.e., neratinib, lapatinib) also have FDA approval and overall survival data in the previously treated metastatic setting. No

head to head trials are available comparing tucatinib (Tukysa) to other tyrosine kinase inhibitors in this space.

IV. Given the population included in the HER2CLIMB trial consisted of heavily pretreated patients, criteria for coverage is set to reflect this patient population. Patients with CNS metastases, however, require only ≥1 prior anti-HER2-based regimen given limited treatment options and lack of strong data with other therapies in this population.

Investigational or Not Medically Necessary Uses

I. Tucatinib (Tukysa) has not been sufficiently studied for safety or efficacy for the following indication(s):
   A. Metastatic colorectal cancer, RAS wild-type, HER2+
      i. HER2 is overexpressed in 3-5% of patients with mCRC and in 10% of patients with RAS wild type mCRC. Tucatinib (Tukysa) with trastuzumab is the first FDA-approved treatment, under accelerated approval, for HER2-positive RAS wild-type unresectable or metastatic colorectal cancer (mCRC) with progression following treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.
      ii. Tucatinib was studied in a phase II, open-label, cross over multicenter trial. The trial was initially designed as a single arm study with 45 participants enrolled to receive tucatinib 300mg orally twice daily with trastuzumab (loading dose of trastuzumab 8mg/kg IV on day 1 of cycle 1, maintenance dose of trastuzumab 6mg/kg on day 1 of each subsequent 21 day cycle). The trial was then expanded globally to include patients who were randomly assigned to receive tucatinib plus trastuzumab (cohort B, N=41) or tucatinib monotherapy (cohort C, N=31). Cohort C was allowed to cross over from tucatinib monotherapy to tucatinib + trastuzumab combination therapy was allowed after 12 weeks if there was disease progression at any time. All participants had to have HER2-positive, RAS wildtype, unresectable or metastatic CRC and received prior treatment with fluoropyrimidines, oxaliplatin, irinotecan, and anti-vascular endothelial growth factor (VEGF) monoclonal antibody, and anti-PD-1 therapy. Participants were not allowed to have received prior anti-HER2 targeting therapy. Participants were treated until disease progression or unacceptable toxicity. The median age was 55 years, 14% of participants were >65 years, 67% white, 61% male, 70.2% of participants had lung metastases, 64.3% had lung metastases. Ninety-nine percent of participants received prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan, 83% and 52% received anti-VEGF antibodies and anti-EGFR antibodies.
      iii. The primary outcome was overall response rate (ORR) with secondary endpoints of duration of response, progression-free survival, overall survival and adverse events. After a median follow-up of 20.7 months, efficacy was evaluated in 84 patients. Cohort A and B had a confirmed ORR per blinded independent central review (BICR) of 38.1%, median duration of response 12.4 months, median PFS of 8.2 months (95% CI, 4.2-10.3), and a median OS of 24.1 months (95% CI, 20.3-36.7). Results for the secondary end points showed a median PFS of 8.2 months

(95% CI, 4.2-10.3), and a median OS of 24.1 months (95% CI, 20.3-36.7), in the combination cohorts.

iv. The most common grade ≥ 3 toxicity was hypertension (7%), ALT elevation (3%), AST elevation (2%), hypertransaminasemia (1%). There were no deaths related to toxicity.

v. As of March 2023, current subsequent therapy recommendations for HER2-amplified RAS wild-type mCRC after progression following treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy are based on limited evidence. NCCN guidelines currently recommend trastuzumab with tucatinib (or pertuzumab (Perjeta) or lapatinib (Tykerb)) if the patient has not had prior HER2 treatment (category 2A recommendation). NCCN guideline directed therapies, trastuzumab with pertuzumab (Perjeta) or lapatinib (Tykerb), for HER2-positive RAS wild-type mCRC are not FDA approved and considered off-label use. After progression following treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, NCCN guidelines recommend trifluridine and tipiracil (Lonsurf) and regorafenib (Stivarga) for mCRC irrespective of HER2 and KRAS mutations and encorafenib (Braftovi) for mCRC in combination with cetuximab (Erbitux) for mCRC with BRAF V600E mutation. Trifluridine and tipiracil (Lonsurf), regorafenib (Stivarga), and encorafenib (Braftovi) are FDA approved for treatment of mCRC.

vi. There is unknown clinical impact on the overall survival rate, health quality of life, or symptom improvement in participants treated with tucatinib and trastuzumab. Results from this phase II trial may be subjected to confounders and biases due to lack of a comparator and an open-label design. ORR is a surrogate marker and does not directly measure clinical outcomes. Change in ORR does not predict morbidity or mortality outcomes. Confirmatory trials are needed to establish safety and efficacy of tucatinib in mCRC, and therefore coverage for tucatinib (Tukysa) for mCRC is considered experimental and investigational.

vii. Despite the accelerated FDA-approval, continued approval of tucatinib (Tykusa) as a subsequent-line treatment of MCL, remains contingent upon verification of clinical benefit in confirmatory trials. There is an ongoing trial to evaluate tucatinib (Tukysa) in HER2-positive mCRC in the ongoing global, randomized Phase 3 clinical trial (MOUNTAINEER-03), comparing tucatinib (Tukysa) in combination with trastuzumab and mFOLFOX6 with standard of care. This trial is intended to serve as the confirmatory trial that is required as part of the accelerated approval pathway.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Tukysa (tucatinib) [prescribing information]. Bothell, WA: Seagen Inc; January 2023.
2. Murthy RK, Loi S, Okines A, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. N Engl J Med. 2020;382(7):597-609.
3. National Comprehensive Cancer Network. NCCN Guidelines: Breast Cancer. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1419.
4. Seattle Genetics. AMCP Formulary Dossier, Tukysa (tucatinib). April 17, 2020.
5. UpToDate, Inc. Systemic treatment for HER2-positive metastatic breast cancer. UpToDate [database online]. Waltham, MA. Last updated May 06, 2020 Available at: http://www.uptodate.com/home/index.html.
6. UpToDate, Inc. Tucatinib: Drug information. UpToDate [database online]. Waltham, MA. Available at: http://www.uptodate.com/home/index.html.
7. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367(19):1783-91.
8. Seattle Genetics, Inc. Tucatinib Plus Trastuzumab in Patients with HER2+ Colorectal Cancer. Available from: https://clinicaltrials.gov/ct2/show/NCT03043313. NLM identifier: NCT03043313.
9. Strickler JH, Cercek A, Siena S, et al. Additional analyses of MOUNTAINEER: A phase II study of tucatinib and trastuzumab for HER2-positive mCRC [abstract]. Annals of Oncology 2022;33:S808-S869.Seagen - Seagen Announces FDA Accelerated Approval of TUKYSA® (tucatinib) in Combination with Trastuzumab for People with Previously Treated RAS Wild-Type, HER2-Positive Metastatic Colorectal Cancer; 2023; accessed 02/15/2023.
10. FDA Approves Expanded Indication of Seagen's Tukysa for Metastatic Colorectal Cancer. IPD Analytics. Accessed November 10, 2022. https://www.ipdanalytics.com/
11. National Comprehensive Cancer Network. NCCN Guidelines: Rectal Cancer. Available at: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Updated 01/25/2023.
12. National Comprehensive Cancer Network. NCCN Guidelines: Colon Cancer. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Updated 01/25/2023.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
lapatinib (Tykerb)	Breast cancer
neratinib (Nerlynx)	Breast cancer, early stage, HER2-positive, following trastuzumab
	Breast cancer, advanced or metastatic HER2-positive
gonadotropin-releasing hormone (GnRH)	Advanced breast cancer in premenopausal women
regorafenib (Stivarga)	Colorectal cancer, metastatic, previously treated
encorafenib (Braftovi), binimetinib (Mektovi)	Colorectal cancer, metastatic, BRAF V600E mutation, combination therapy
trifluridine/tipiracil (Lonsurf)	Colorectal cancer, metastatic, previously treated

Policy Implementation/Update

Action and Summary of Changes	Date
Policy updated to include MOUNTAINEER trial results in E/I section for metastatic colorectal cancer. Updated policy formatting. Added related policies. Updated supporting evidence, references.	03/2023
Policy created	08/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP034

Description

Glycerol phenylbutyrate (Ravicti) and sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva) are orally administered nitrogen-binding agents used in the treatment of urea cycle disorder (UCD).

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
sodium phenylbutyrate (generic Buphenyl)	Urea Cycle Disorder	500mg tablets	1200 tablets/30 days[∞]
		3g/tsp powder (250g bottle)	600 grams/30 days[∞]
sodium phenylbutyrate (Buphenyl)		500mg tablets	1200 tablets/30 days[∞]
		3g/tsp powder (250g bottle)	600 grams/30 days[∞]
sodium phenylbutyrate (Pheburane)		Oral pellets (84g bottle)	600 grams/30 days[∞]
glycerol phenylbutyrate (Ravicti)		1.1g/mL (25mL bottle)	525 mL (570g)/30 days[*]
sodium phenylbutyrate (Olpruva)		2 gm packets for suspension	90 packets/30 days
		3 gm packets for suspension	
		4 gm packets for suspension	
		5 gm packets for suspension	
		6 gm packets for suspension	
		6.67 gm packets for suspension	

*Glycerol phenylbutyrate (Ravicti) max dose of 17.5ml/day (no more than 19 g/day)

[∞]Sodium phenylbutyrate (Buphenyl, Pheburane) max dose of 20g/day

Initial Evaluation

I. **Sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva)** may be considered medically necessary when the following criteria below are met:

A. Member is diagnosed with **Urea Cycle Disorder (UCD)** when the following are met:

1. Management by dietary protein restriction and amino acid supplementation alone has been ineffective; **AND**

2. Member will continue dietary protein restriction and, if needed, amino acid supplementation; **AND**
3. Documentation of baseline ammonia level indicating member has hyperammonemia (ammonia level is above the upper limit of normal based on member's age); **OR**
    i. Member is transitioning from IV amino acid infusion (sodium phenylacetate/sodium benzoate) to oral therapy; **AND**

B. Treatment with generic sodium phenylbutyrate has been ineffective, contraindicated, or not tolerated; **AND**

C. Member must demonstrate a medical reason they are unable to utilize generic sodium phenylbutyrate. Convenience of administration route or palatability preference does not equate to medical necessity (documentation required); **AND**
    1. For brand sodium phenylbutyrate (Buphenyl) tablets:
        i. Member weighs at least 20 kg (44 lbs.)

II. **Glycerol phenylbutyrate (Ravicti)** may be considered medically necessary when the following criteria below are met:
    A. Member meets criteria IA-IB; **AND**
    B. Member must demonstrate a medical reason they are unable to utilize sodium phenylbutyrate products (Buphenyl, Pheburane, Olpruva). Convenience of administration route or palatability preference does not equate to medical necessity (documentation required).

III. Glycerol phenylbutyrate (Ravicti), sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva) are considered investigational when used for all other conditions, including but not limited to:
    A. Amyotrophic lateral sclerosis (ALS)
    B. Acute hyperammonemia
    C. N-acetylglutamate synthase (NAGS) deficiency

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Provider attestation member will be continuing dietary protein restriction and, if needed, amino acid supplementation; **AND**

IV. Member has exhibited a reduction from baseline in plasma ammonia levels; **OR**
    A. Member has maintained a plasma ammonia level within normal range for member's age (see supporting evidence for normal ranges)

Supporting Evidence

I. Urea cycle disorders (UCD) are rare genetic metabolic deficiencies caused by missing enzymes in the urea cycle, the most common being ornithine transcarbamylase (OTC) deficiency. All of the following are known UCDs: carbamylphosphate synthetase I [CPS1], ornithine transcarbamylase [OTC], argininosuccinic acid synthetase [ASS1], argininosuccinic acid lyase [ASL], arginase [ARG], and N-acetyl glutamate synthetase [NAGS]. In UCD, the body is unable to convert the excess amino acids from food breakdown into uric acid that is secreted from the body resulting in high levels of ammonia in the body. In most cases, onset of symptoms occurs at, or shortly following, birth (neonatal period); however, some individuals may not exhibit hyperammonemia or symptoms until later during infancy, childhood, or even adulthood due to a partial enzyme deficiency. It is important that the diagnosis and treatment be started early to improve survival.

II. An elevated plasma ammonia level of 150 µmol/L (>260 µg/dl), or higher, in neonates and > 100 µmol/l (175 µg/dl) in older children and adults, is a strong indication for the presence of a urea cycle disorder. Hyperammonemia can be the first symptom in patients without a known family history of UCD or without knowing the patient's genetics. Normalization of ammonia levels is critical to prevent neurologic abnormalities and impaired cognitive function in hyperammonemia. Acute management includes hemodialysis, fluid management, and IV infusion of sodium phenylacetate-sodium benzoate. Once patients are stabilized (ammonia level <100 mmol/L and mental status returns to baseline), patients can transition to oral therapy (sodium phenylbutyrate or glycerol phenylbutyrate). Per Orphanet Guidelines for Rare Diseases, not all patients who recover from an episode of hyperammonemia require chronic nitrogen-scavenging agents, but they should be considered if the patient cannot manage the disease with dietary treatment alone.

III. The goal of long-term management of UCD are to prevent hyperammonemia and includes dietary restrictions of protein, use of specialized formulas (in infants and young children), and oral nitrogen-scavenging agents. Sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva) and glycerol phenylbutyrate (Ravicti) and are nitrogen-binding agents used in the chronic management of patients with UCD involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS), that cannot be managed by dietary protein restriction and/or dietary supplementation alone. Treatment must be combined with dietary protein restriction and, in some cases, dietary/amino acid supplementation (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements). Poor adherence with prescribed diets may increase the patient's protein intake, which may necessitate a dosage increase; therefore, attestation of continuing dietary protein restriction and/or, amino acid supplementation is required.

IV. Sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva) has more real-world data due to the time on the market as sodium phenylbutyrate was approved in 1996 and glycerol phenylbutyrate (Ravicti) was not approved until 2013. Sodium phenylbutyrate (Pheburane) was approved via 505(b)(2) pathway in 2022 and shares the same indication as Buphenyl. There have been several head-to-head non-inferiority studies in both adults and pediatrics, that showed glycerol phenylbutyrate (Ravicti) is as effective as sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva) in treating UCD and has a slightly improved tolerability overall (no salty taste and odorless). Although, there is more data in the use of sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva) and because it is specifically indicated in ornithine transcarbamylase (OTC)

therapy, the most common UCD; sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva) is typically started if UCD is suspected, and a genetic profile has not yet been completed. Additionally, in the absence of a clinically significant difference in efficacy between glycerol phenylbutyrate (Ravicti) and sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva), generic sodium phenylbutyrate is chosen as the preferred agent in the setting of UCD due to generic availability, cost, and a larger pool of safety and efficacy data.

V. Documentation of medical necessity for glycerol phenylbutyrate (Ravicti) and sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva) is required, as the recommended dose can be obtained with the generic sodium phenylbutyrate, providing a significant price differential (3 – 10x difference). Acceptable rationale for medical necessity include difficulty swallowing, restricted sodium intake, etc. Convenience of administration route or palatability preference does not equate to medical necessity.

VI. The notable differences between glycerol phenylbutyrate (Ravicti) and sodium phenylbutyrate (Buphenyl) is the unpleasant smell/taste and the higher than the recommended daily allowance of sodium in sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva). Sodium phenylbutyrate products should be used with caution in patients who have conditions that cause edema and/or must maintain restricted sodium intake (congestive heart failure, severe renal insufficiency, cirrhosis, or nephrosis). It is recommended that patients that develop new onset edema or worsening edema with sodium phenylbutyrate discontinue sodium phenylbutyrate products. Furthermore, generic sodium phenylbutyrate and brand sodium phenylbutyrate (Buphenyl) are both available in tablet and powder formulations and are known to have a distinct, strong salty taste. Glycerol phenylbutyrate (Ravicti) is available as a tasteless/odorless oral solution. Sodium phenylbutyrate (Pheburane) shares the same indication as generic sodium phenylbutyrate and Buphenyl, however is formulated as tasteless/odorless oral pellets. Generic sodium phenylbutyrate powder, Buphenyl powder, and glycerol phenylbutyrate (Ravicti) are able to be administered via nasogastric or gastrostomy tube.

VII. Clinical study results showed ammonia values ranged from 9-35 µmol/L; however, the US UCD management guidelines do not specify a direct chronic ammonia treatment target number. Additionally, the normal value changes from neonates, to pediatrics, to adults and the consensus would be to focus on keeping the body within the normal range for the patient's age on the lab test used, see below table.

Ammonia Level Range Table	
Age Range	**Normal Ammonia Range**
Adults	7-35 mmol/L
Children	28-57 mmol/L
Newborns	64-107 mmol/L

VIII. The quantity limits noted in the table above reflect the maximum daily dose for each agent as there have not been safety/efficacy data over these doses. If the patient is transitioning from sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva) to glycerol phenylbutyrate (Ravicti), a slight initial dosage change to ensure the patient is receiving the same amount of phenylbutyric acid, is required. See appendix for details.

Investigational or Not Medically Necessary Uses

I. Amyotrophic Lateral Sclerosis (ALS)

A. In a phase 2 clinical study (CENTAUR), 137 patients with ALS were randomized 2:1 to receive sodium phenylbutyrate combined with taurursodiol (PB-TURSO) [N=89] or placebo [N=48], for 6 months. The primary endpoint was the ability to slow the disease progression as measured by changes in the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R). The ALSFRS-R is the principal functional end point referenced in the latest FDA guidance for ALS trials with each point decrease representing lost capability across a 12 point scale, looking at tasks such as breathing, walking, fine motor skills; a higher score meaning higher normal function and less progressed disease symptoms. The primary endpoint was the only endpoint to reach statistical significance with a p-value of 0.03 and a mean rate of change in the ALSFRS-R scores of -1.24 points per month for PB-TURSO versus -1.66 points in placebo. With an absolute mean difference at week 24 of 2.32 in PB-TURSO versus placebo correlating to preserved functioning ability in those taking the study compound over placebo.

B. An open-label extension (OLE) was allowed for those who completed the CENTAUR trial (97 patients in total between both arms) for up to 30 months. Fifty-six patients on PB-TURSO and 34 on placebo enrolled, all receiving PB-TURSO in the OLE, those originally on placebo were changed over. The risk of key events including death, tracheostomy, first hospitalization and progression-free survival were all evaluated. Median key event-free survival duration was 4.8 months longer in participants originally randomized to PB-TURSO versus placebo, and median tracheostomy/PAV-free survival duration was 7.3 months longer. As of the analysis cut-off, median time to first hospitalization was not yet reached in the group originally randomized to PB-TURSO, compared with 14.1 months in the group originally randomized to placebo.

C. The OLE noted that this added to the previously reported overall functional/survival benefits from the primary phase 2 randomized, blinded trial. On September 7th, a second FDA advisory panel met to discuss the phase 2 and OLE data, as the March panel negatively reviewed this data pushing back the first PDUFA date by several months. On September 7th, the committee was 7-2 favorable, changing their prior decision. Currently, there is a recruiting phase 3 trial (PHOENIX) and a PDUFA date on September 29th. If approved, PB-TURSO would be an add-on agent to those already approved in the treatment of ALS, riluzole, and edaravone. At this time, sodium phenylbutyrate is considered experimental and investigational for the treatment of ALS.

II. Acute hyperammonemia

A. Neither glycerol phenylbutyrate (Ravicti) nor sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva) are indicated to treat acute hyperammonemia, which is considered a life-threatening emergency. Rapidly acting interventions are essential to reduce plasma ammonia levels. Treatment of acute hyperammonemia includes stopping protein intake, hydration, and initiation of IV arginine hydrochloride, sodium benzoate/sodium phenylacetate (Ammonul), and/or oral citrulline.

III. N-acetylglutamate synthase (NAGS) deficiency

A. The efficacy and safety of glycerol phenylbutyrate (Ravicti) for the treatment of hyperammonemia due N-acetylglutamate synthase (NAGS) deficiency has not been established.

Appendix

I. The recommended dosages for patients that are treatment naïve or switching from sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva) to phenylbutyrate (Ravicti) are different. A direct conversion of dosing can be calculated for patients already on sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva) to sodium phenylbutyrate (Ravicti):
    a. Total daily dose glycerol phenylbutyrate (mL) = 0.8 x total daily dose of sodium phenylbutyrate (grams)

References

1. Ravicti [Prescribing Information]. South San Francisco, CA: Hyperion Therapeutics Inc.; September 2021.
2. Buphenyl [Prescribing Information]. Ucyckyd Pharma, Inc
3. Pheburane [Prescribing Information]. Lucane Pharma.; June 2022.
4. Häberle J, Burlina A, Chakrapani A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders: first revision. *J of Inher Metab Disea.* 2019;42(6):1192-1230.
5. Häberle J, Boddaert N, Burlina A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders. *Orphanet J Rare Dis.* 2012;7:32. doi:10.1186/1750-1172-7-32
6. Lee B, Diaz GA, Rhead W, et al. Blood ammonia and glutamine as predictors of hyperammonemic crises in patients with urea cycle disorder. *Genetics in Medicine.* 2015;17(7):561-568.
7. Lee B. Urea cycle disorders: clinical features and diagnosis. In: Post TW, ed. UpToDate. UpToDate; 2022. Accessed September 07, 2022. https://www.uptodate.com/contents/urea-cycle-disorders-clinical-features-and-diagnosis
8. Lee B. Urea cycle disorders: management. In: Post TW, ed. UpToDate. UpToDate; 2022. Accessed September 07, 2022. https://www.uptodate.com/contents/urea-cycle-disorders-management.
9. Paganoni, S, Hendrix, S, Dickson, SP, et al. Trial of sodium phenylbutyrate-taurursodiol for amyotrophic lateral sclerosis. *New Engl J Med*. 2020; 383: 919-30 DOI: 10.1056/NEJMoa1916945
10. Paganoni S, Hendrix S, Dickson SP, et al. Effect of sodium phenylbutyrate/taurursodiol on tracheostomy/ventilation-free survival and hospitalisation in amyotrophic lateral sclerosis: long-term results from the CENTAUR trial. *J Neurol Neurosurg Psychiatry.* 2022 May 16;93(8):871–5. doi: 10.1136/jnnp-2022-329024. Epub ahead of print. PMID: 35577511.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
carbaglu (carglumic acid)	Acute hyperammonemia due to NAGS deficiency
	Chronic hyperammonemia due to NAGS deficiency
	Acute hyperammonemia due to PA or MMA

Policy Implementation/Update

Action and Summary of Changes	Date
Added new product, sodium phenylbutyrate (Olpruva) to policy.	06/2023
Added new product, sodium phenylbutyrate (Pheburane) to policy. Added generic sodium phenylbutyrate to QL table. Expanded on quantity limits to meet weight-based dosing. Updated formatting to separate generic SPB, Buphenyl, Pheburane, and Ravicti. Removed age requirement. Removed ammonia lab requirement in initial criteria and replaced with documentation of baseline level, allow coverage in members transitioning from IV to oral therapy; added requirement of documentation of medical necessity for branded products; added attestation for continuing amino acid supplementation/diet in renewal, added NAGS to E/I and updated E/I evidence. Updated supporting evidence and references. Added appendix and related policies section.	09/2022

Updated policy name, added second medication to the policy, sodium phenylbutyrate. Expanded on quantity limits to meet weight-based dosing; added clinical criteria for review of sodium phenylbutyrate. Updated renewal criteria. Added ALS as experimental indication. Revised and strengthened the supporting evidence.	12/2021
Criteria update: Included new FDA expanded indication for pediatric patients 2 months and older. Glycerol phenylbutyrate (Ravicti) was originally approved for pediatric patients 2 years and older. Additionally, a question was added to the renewal portion of this policy to assess for toxicity.	01/2019
Previous Reviews	07/2013; 08/2013

Policy Type: PA/SP Pharmacy Coverage Policy: UMP216

Description

Uridine triacetate (Xuriden) is a pyrimidine analog for uridine replacement indicated in adult and pediatric patients for the treatment of hereditary orotic aciduria (HOA).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
uridine triacetate (Xuriden)	2 g/packet	Hereditary orotic aciduria	240 g/30 days

Initial Evaluation

I. Uridine triacetate (Xuriden) may be considered medically necessary when the following criteria are met:
   A. Member is diagnosed with **hereditary orotic aciduria (HOA)** by a provider specializing in the patient's diagnosis or in consultation with a geneticist, hematologist or specialist in metabolic disorders; **AND**
   B. Member has at least ONE of the following diagnostic criteria:
      1. Molecular genetic test indicating variations in uridine monophosphate synthetase (UMPS) gene; **OR**
      2. Urine test indicating high levels of orotic acid and/or orotidine; **AND**
   C. Member has severe disease as defined by one or more of the following:
      1. Hematologic abnormalities (e.g. megaloblastic anemia, neutropenia, leukopenia); **OR**
      2. Renal tract obstruction (due to aggregation of orotic acid crystals); **OR**
      3. Immune dysfunction; **OR**
      4. Congenital anomalies; **OR**
      5. Physical and intellectual developmental delays; **AND**
   D. Provider attestation that member does not have ornithine transcarbamoylase (OTC) deficiency; **AND**
      1. Blood ammonia levels are within normal limits

II. Uridine triacetate (Xuriden) is considered investigational when used for all other conditions, including but not limited to:
   A. Fluoropyrimidine overdose/overexposure

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Prescriber attestation that the member has exhibited stability or improvement in disease symptoms [e.g., improvement in hematologic status, improvement in growth]

Supporting Evidence

I. HOA is an extremely rare genetic disorder affecting both men and women, with fewer than 25 cases of patients with this disorder worldwide have been reported in the medical literature. It is caused by variations in the uridine monophosphate synthase (UMPS) gene which is responsible for producing an enzyme that catalyzes the last two steps of the pyrimidine biosynthesis pathway. One of these two final steps is to convert orotic acid into another chemical substance. Because of the variation in the UMPS gene, individuals with this disorder have low levels of the enzyme needed to breakdown orotic acid and subsequently have a reduced production of uridine, a nucleotide involved in multiple essential physiological functions including biosynthesis of RNA, synthesis of glycogen and glycoprotein, phospholipid synthesis, and DNA synthesis.
II. The exact mechanism by which orotic acid buildup and uridine monophosphate synthase deficiency leads to signs and symptoms of the disease is not completely understood. Orotic acid is believed to improve the metabolism of folic acid and vitamin B12 and may play a role in gene transcription.
III. HOA is a clinically heterogenous disorder and individuals who retain some UMPS activity may be asymptomatic or only mildly affected. Features of more severe disease include megaloblastic anemia that is not responsive to treatment with vitamin B12 or folic acid, neutropenia, renal tract obstruction (due to aggregation of orotic acid crystals), immune dysfunction, congenital anomalies, and physical and intellectual developmental delays.
IV. Diagnosis of HOA is confirmed by assessment of symptoms, family history, a urine test indicating high levels of orotic acid and/or orotidine, and a molecular genetic test indicating variations in uridine monophosphate synthetase (UMPS) gene. Not all patients will present with elevated orotic acid and/or orotidine urine levels; however, this is the most common laboratory abnormality seen in 80%-99% of patients. Deferential diagnosis of HOA includes urea cycle disorders one of which may also present with high blood levels of orotic acid, this disorder is known as ornithine transcarbamoylase (OTC) deficiency. OTC can be distinguished from HOA by evaluation of blood ammonia levels. Patients with HOA will have normal blood ammonia levels, whereas, patients with OTC deficiencies tend to have elevated ammonia levels.
V. Nucleotide replacement has been the mainstay of treatment of HOA. Case reports document rapid hematologic response with administration of uridine. Some patients treated with uridine have reached adulthood and some who have been treated with uridine lifelong have fathered or given birth to normal children. Supportive therapies include blood transfusions, intravenous hydration and electrolyte replacement, and treatment for renal and infectious disease complications.

VI. FDA approval of uridine triacetate (Xuriden) was based on collective evidence from case reports, pharmacokinetic studies, safety studies, and one Phase III, open-label, single-arm, six-week clinical trial and its six-month extension phase. The efficacy was evaluated in a Phase III trial which enrolled four patients with HOA (three male, one female; age range three to 19 years). Three patients were previously treated with uridine and were switched to uridine triacetate (Xuriden). One patient was treatment naïve. The study evaluated stability or improvement in patients' hematologic parameters in the initial six-week period and the extension phase. By week six, three previously treated patients met the primary endpoint and maintained stability of their hematologic parameters, while one treatment naïve patient failed to meet the primary endpoint – improvement in hematologic parameters. The secondary endpoint was improved growth parameters (height and weight). Effect on growth was assessed in three patients and remained unchanged after 24 months of treatment.

VII. Uridine triacetate (Xuriden) is the only FDA approved therapy for HOA. The National Organization for Rare Disease Disorders and other expert opinions recommend treatment with uridine triacetate (Xuriden).

VIII. Uridine triacetate (Xuriden) should not be used for the treatment of fluoropyrimidine overdose/overexposure. A different formulation of uridine triacetate (Vistogard) has been approved by the FDA for the treatment of this condition.

Investigational or Not Medically Necessary Uses

I. Uridine triacetate (Xuriden) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
    A. Fluoropyrimidine overdose/overexposure

References

1. Xuriden [Prescribing Information]. Wellstat Therapeutics Corporation: Rockville, MD. September 2015.
2. FDA. Xuriden (uridine triacetate) oral granules. Medical Review Letter. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208169Orig1s000TOC.cfm. Accessed December 30, 2020.
3. National Organization for Rare Disorders. Hereditary Orotic Aciduria. Available at https://rarediseases.org/rare-diseases/hereditary-orotic-aciduria/. Accessed December 30, 2020.
4. Wellstat Therapeutics. Open-Label Study of Uridine Triacetate in Pediatric Patients with Hereditary Orotic Aciduria. Available at https://clinicaltrials.gov/ct2/show/NCT02110147. Accessed December 30, 2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	01/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP223

Split Fill Management*

Description

Vandetanib (Caprelsa) is an orally administered kinase inhibitor, with activity at VEGF, EGFR, and RET kinases.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
vandetanib (Caprelsa)	100 mg tablets	Locally advanced or metastatic medullary thyroid cancer	60 tablets/30 days
	300 mg tablets		30 tablets/30 days

Initial Evaluation

I. Vandetanib (Caprelsa) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist or endocrinologist; **AND**
   C. A diagnosis of **unresectable locally advanced or metastatic (stage III or IV) medullary thyroid cancer** when the following is met:
      1. Medication is not used in combination with any other oncology therapy.

II. Vandetanib (Caprelsa) is considered investigational when used for all other conditions, including but not limited to:
   A. Anaplastic Thyroid Carcinoma
   B. Biliary tract cancer
   C. Breast cancer
   D. Follicular Thyroid Carcinoma
   E. Glioblastoma
   F. Ovarian cancer
   G. Renal cell carcinoma
   H. Urothelial cancer
   I. Non-small cell lung cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication is prescribed by, or in consultation with, an oncologist or endocrinologist; **AND**
IV. Will not be used with any other oncology therapy; **AND**
V. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread.

Supporting Evidence

I. Vandetanib (Caprelsa) is a kinase inhibitor with activity at multiple kinases. *In vitro* studies show that vandetanib (Caprelsa) inhibits the activity of epidermal growth factor receptor (EGFR) family, vascular endothelial growth factor (VEGF) receptors, rearranged during transfection (RET), protein tyrosine kinase 6, TIE2, members of the EPH receptors kinase family, and members of the Src family of tyrosine kinases. In mouse models, vandetanib (Caprelsa) reduced tumor cell growth and metastasis.
II. Vandetanib (Caprelsa) was studied in a Phase 3, double blind, placebo controlled, randomized trial (ZETA) in 331 patients with symptomatic or progressive unresectable locally advanced or metastatic medullary thyroid cancer. There is currently no evidence that it is safe and effective in treating other types of cancer.
III. The ZETA trial evaluated treatment with vandetanib (Caprelsa) as monotherapy versus placebo. Patients in the trial had either hereditary, sporadic, or unknown, or metastatic disease type. Fifty nine percent of patients had a RET positive mutation while 40% had unknown RET mutation. Patients were excluded from treatment if they had significant cardiac, hematopoietic, hepatic, or renal dysfunction, were treated with chemotherapy and/or radiation therapy within four weeks of treatment with vandetanib (Caprelsa) or were taking any concomitant medications that may have affected QTc or induced CYP3A4 function.
IV. The primary endpoint evaluated in the ZETA trial was progression free survival (PFS). There was a statistically significant improvement in PFS for patients randomized to vandetanib (Caprelsa). The number of events in vandetanib (Caprelsa) arm was 59 (26%) and 41 (41%) in the placebo arm with a Hazard Ratio (HR) = 0.35; 95% Confidence Interval (CI) = 0.24-0.53; p<0.001. The median survival in months for the placebo arm was 16.4 while for the vandetanib (Caprelsa) arm the median survival was not reached at the time of analysis;, however, the predicted median survival was 30.5 months. The mature data for overall survival (OS) was studied as a secondary endpoint and was similar between both treatment arms at 81.6 months for vandetanib (Caprelsa) and 80.4 months for placebo arm. However, OS survival data was not powered and was confounded by patients from the placebo arm that were eligible to start treatment with vandetanib (Caprelsa) after conclusion of the study. Other secondary endpoints evaluated included objective response rate (ORR) and disease control rate, both of which reached

statistical significance when compared to placebo. Quality of life and pain reduction outcomes were not reported or could not be evaluated.

V. Fifty-five percent (55%) of the patients on the vandetanib (Caprelsa) arm experienced grade 3 or 4 adverse events. Adverse reactions resulting in death occurred in five patients treated with vandetanib (Caprelsa) due to respiratory failure, respiratory arrest, aspiration pneumonia, cardiac failure with arrhythmia, and sepsis. Causes of discontinuation in vandetanib (Caprelsa)-treated patients in >1 patient included asthenia, fatigue, rash, arthralgia, diarrhea, hypertension, prolonged QT interval, increase in creatinine, and pyrexia. Serious adverse events in vandetanib (Caprelsa) treated patients in >2% of patients included diarrhea, pneumonia, and hypertension. Patients receiving vandetanib (Caprelsa) experienced a mean prolongation of their QT interval of 35ms, and sudden death and torsades des pointes have been observed with vandetanib (Caprelsa). A Risk Evaluation and Mitigation Strategy (REMS) is used to decrease the risk of these adverse events.

VI. Vandetanib (Caprelsa) has a Category 1 recommendation by the National Comprehensive Cancer Network (NCCN) guidelines for the treatment of recurrent or persistent medullary thyroid carcinoma and joins cabozantinib (Cabometyx) and selpercatinib (Retevmo) in the list of preferred systemic regimens. It is also recommended as the first line treatment option by the American Thyroid Association Guidelines. Vandetanib (Caprelsa) should be prescribed in consultation with, or by, an oncologist or endocrinologist for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. Use of vandetanib (Caprelsa) in patients with indolent, asymptomatic, or slowly progressive disease should only be considered after examining the treatment related risks of this agent.

Investigational or Not Medically Necessary Uses

I. Vandetanib (Caprelsa) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Anaplastic Thyroid Carcinoma
   B. Biliary tract cancer
   C. Breast cancer
   D. Follicular Thyroid Carcinoma
   E. Glioblastoma
   F. Ovarian cancer
   G. Renal cell carcinoma
   H. Urothelial cancer
   I. Non-small cell lung cancer

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Caprelsa (vandetanib) [package insert]. Cambridge, MA: Sanofi Genzyme; December 2016.
2. Wells, SA, Jr., Robinson, BG, Gagel, RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol. 2012 Jan 10;30(2):134-41. PMID: 22025146
3. Haddad RI, Bischoff L, Bernet V, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Thyroid Carcinoma. Available at https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf. Accessed January 3, 2021.
4. Wells SA Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015;25(6):567-610. doi:10.1089/thy.2014.0335
5. Thornton K, Kim G, Maher VE, et al. Vandetanib for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease: U.S. Food and Drug Administration drug approval summary. Clin Cancer Res. 2012;18(14):3722-3730. doi:10.1158/1078-0432.CCR-12-0411

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy was updated and transitioned from an old criteria to a new format Removal of criteria requirements that are managed by provider (drug-drug interactions, REMS program, monitoring of CrCl, QT prolongation, hepatic impairments, hypertension, and other aspects from labeled warnings and precautions)	02/2021
Criteria created	02/2012

Policy Type: PA/SP Pharmacy Coverage Policy: UMP071

Description

Venetoclax (Venclexta) is an orally administered B-cell lymphoma-2 (BCL-2) inhibitor.

Length of Authorization

- Initial:
  - i. Previously untreated CLL/SLL: 12 months
  - ii. All other indications: Six months
- Renewal:
  - i. Previously untreated CLL/SLL: Cannot be renewed
  - ii. All other indications: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
venetoclax (Venclexta)	Starter Pack	Chronic lymphocytic leukemia (CLL); Small lymphocytic lymphoma (SLL)	1 pack/28 days
	10 mg tablets		28 tablets/28 days
	50 mg tablets		28 tablets/28 days
	100 mg tablets		120 tablets/30 days
	100 mg tablets	Acute myeloid leukemia	180 tablets/30 days

Initial Evaluation

I. Venetoclax (Venclexta) may be considered medically necessary when the following criteria below are met:
   A. Prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   B. A diagnosis of:
      1. **Relapsed/refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)**; **AND**
         i. Received at least one prior therapy [e.g., Imbruvica (ibrutinib) or chemotherapy-containing regimen]; **AND**
         ii. Will be used as monotherapy or in combination with rituximab (Rituxan); **OR**
      2. **Previously untreated chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL); AND**
         i. Will be used in combination with obinutuzumab (Gazyva);**OR**
      3. **Newly-diagnosed acute myeloid leukemia (AML)**; **AND**
         i. Age 75 years and older; **OR**
         ii. Have comorbidities that preclude use of intensive induction chemotherapy such as:

a. Baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2-3
b. Severe cardiac or pulmonary comorbidity
c. Moderate hepatic impairment
d. CrCL ≥30 to <45 mL/min; **AND**

iii. Used in combination with azacitidine or decitabine or low-dose cytarabine

II. Venetoclax (Venclexta) is considered investigational for all other conditions, including but not limited to:
A. Acute Myeloid Leukemia – Previously treated
B. Multiple Myeloma (MM)
C. Previously untreated CLL/SLL – Treatment for more than 12 months

Renewal Evaluation

I. Member has a diagnosis of relapsed/refractory CLL/SLL or newly diagnosed AML; **AND**
II. Clinical documentation of response to treatment, such as stabilization or improvement of disease; **AND**
III. Absence of unacceptable toxicity from the medication

Supporting Evidence

I. Venetoclax (Venclexta) is FDA-approved for the treatment of CLL/SLL, in adult patients with or without 17p deletion.
II. Patients included in venetoclax (Venclexta) monotherapy studies in CLL/SLL were relapsed/refractory to fludarabine-based regimens (e.g. Rituximab+Fludarabine+Cyclophosphamide, Fludarabine+Rituximab, Fludarabine+Cyclophosphamide) or alkylator- based regimens (e.g. chlorambucil, bendamustine), or to ibrutinib (Imbruvica) or idelasilib (Zydelig). Patients included in the venetoclax (Venclexta) plus rituximab (Rituxan) trial (MURANO) for relapsed CLL/SLL had received one to three previous treatments (including at least one chemotherapy-containing regimen). Prior radiation therapy or stem cell transplant alone is not considered a prior therapy as this treatment strategy alone was not considered an inclusion in pivotal trials.
III. Venetoclax (Venclexta) approval in untreated CLL/SLL was based on the findings from the CLL14 randomized, open label, phase 3 trial. CLL14 evaluated the safety and efficacy of fixed-duration treatment with venetoclax (Venclexta) in combination with obinutuzumab (VEN+G) versus obinutuzumab in combination with chlorambucil (GClb) for patients with previously untreated CLL with coexisting medical conditions. Patients received 12 months of venetoclax (Venclexta) in combination with six cycles of obinutuzumab. The trial met its primary outcome of progression-free survival (PFS) in patients treated with Venclexta plus obinutuzumab compared to patients who received chlorambucil plus obinutuzumab, a commonly used standard of care. After a median follow-up of 28 months, Venclexta plus obinutuzumab reduced the risk of progression or death by 67% compared with chlorambucil plus obinutuzumab (hazard ratio: 0.33, 95%

confidence interval [CI]: 0.22, 0.51; p<0.0001). The majority of patients receiving Venclexta in the trial remained progression-free at two years.

IV. FDA granted accelerated approval to venetoclax (Venclexta) for use in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of adult patients with newly-diagnosed acute myeloid leukemia (AML) who are aged 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. Initial FDA-approval was based on two phase Ib/II trials in this setting. The findings from these trials were consolidated by phase III confirmatory studies (VIALE-A and VIALE-C).

V. Venetoclax (Venclexta) was studied in a confirmatory phase III randomized (2:1) double-blind, placebo-controlled trial (VIALE-A), which assessed the efficacy and safety of venetoclax (Venclexta) in combination with azacitidine (IV or SQ administration) versus placebo+ azacitidine (n= 431). Participants in this trial had median age of 76 years, intermediate or poor/ high risk AML and at least one comorbidity precluding intensive therapies. At median duration of follow-up (20.5 months, <0.1- 30.7), median overall survival for venetoclax- azacitidine treatment arm was 14.7 months (95% CI; 11.9, 18.7) as compared to that of 9.6 months (95% CI; 7.4, 12.7) for placebo-azacitidine arm (HR 0.66; 95% CI; 0.52-0.85; *p* <0.0001). Additionally, treatment arm (venetoclax- azacitidine) also reported complete remission in 66.4% (95% CI; 60.6, 71.9) versus 28.3% (95% CI; 21.1, 36.3) in placebo-azacitidine arm (*p*<0.001) with 43.4% participants achieving composite complete remission before cycle 2.

VI. In VIALE-C clinical trial, efficacy and safety of venetoclax (Venclexta) in combination with low-dose cytarabine (LDAC) was compared with placebo plus LDAC in an ongoing double-blind, randomized (2:1) phase 3 study. From a pool of 211 randomized study participants (n=143 in treatment arm versus n= 68 in placebo arm), median follow-up of 17.5 months (95% CI; 0.1, 23.5) was reported at data cut-off. Median overall survival (OS) was 8.4 months in the treatment (venetoclax-cytarabine) arm versus 4.1 months in placebo-cytarabine arm (HR 0.70; 95% CI 0.50–0.99; P = 0.04). This OS data was not statistically significant. Additionally, a median event-free survival (EFS) was reported at 4.9 months vs 2.1 months for treatment and placebo arms, respectively (HR 0.61; 95% CI; 0.44, 0.84; *P* = 0.003).

Investigational or Not Medically Necessary Uses

I. Acute Myeloid Leukemia – Previously treated
   A. Pivotal trials leading to FDA approval were specifically in the previously untreated setting. Use in the relapsed/refractory setting is not supported by clinical trials nor cited within NCCN AML guidelines.

II. Multiple Myeloma (MM)
   A. Venetoclax (Venclexta) is currently being evaluated for use in MM and is the subject of ongoing clinical trials. As of March 2019, "FDA reviewed data from the BELLINI clinical trial (NCT02755597, Study M14-031) evaluating the use of Venetoclax (Venclexta) combined with bortezomib and dexamethasone in patients with multiple myeloma. The interim trial results demonstrated an increased risk of death for patients receiving Venetoclax (Venclexta) as compared to the control group. On March 6, 2019, the FDA required no new patients be enrolled on the Bellini trial. The FDA suspended enrollment in other ongoing multiple myeloma clinical trials of Venclexta."

III. Previously untreated CLL/SLL – Treatment for more than 12 months

A. Venetoclax (Venclexta) approval in untreated CLL/SLL was based on the findings from the CLL14 randomized, open label, phase 3 trial. CLL14 evaluated the safety and efficacy of fixed-duration treatment with venetoclax (Venclexta) in combination with obinutuzumab (VEN+G) versus obinutuzumab in combination with chlorambucil (GClb). Patients received 12 months of venetoclax (Venclexta) in combination with six cycles of obinutuzumab. Treatment beyond 12 months has not been evaluated.

References

1. Venclexta [Prescribing Information]. Abbvie Inc.: North Chicago, IL; May 2019.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66(1):7.
3. Food and Drug Administration [Press Release]. FDA approves new drug for chronic lymphocytic leukemia in patients with a specific chromosomal abnormality. Updated 04/11/2016. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm495253.htm. [Accessed 04/18/2016].
4. Genentech [Press Release]. Genentech Announces FDA Grants Venclexta™ (Venetoclax) Accelerated Approval for People with a Hard-To-Treat Type of Chronic Lymphocytic Leukemia. Updated 04/11/2016. Available at: http://www.gene.com/media/press-releases/14623/2016-04-11/genentech-announces-fda-grants-venclexta. [Accessed 04/18/2016].
5. UpToDate, Inc. Clinical presentation, pathologic features, diagnosis, and differential diagnosis of chronic lymphocytic leukemia. UpToDate [database online]. Waltham, MA. Updated 01/14/2016. Available at: http://www.uptodate.com/home/index.html. [Accessed 04/18/2016].
6. UpToDate, Inc. Treatment of relapsed or refractory chronic lymphocytic leukemia. UpToDate [database online]. Waltham, MA. Updated 04/05/2016. Available at: http://www.uptodate.com/home/index.html. [Accessed 04/18/2016].
7. NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 1.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf [Accessed 08/09/2018].
8. National Institutes of Health. Clinical Trials Database. Venetoclax. Available at: https://clinicaltrials.gov/ct2/results?term=venetoclax&Search=Search. [Accessed 04/18/2016].
9. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. N Engl J Med. 2018;378(12):1107-1120.
10. NCCN Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. Version 3.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf
11. Dinardo CD, Pratz K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood. 2018; Epub ahead of print.
12. Clinicaltrials.gov (2018). NCT02242942: A Prospective, Open-Label, Multicenter Randomized Phase III Trial to Compare The Efficacy and Safety of A Combined Regimen of Obinutuzumab and Venetoclax (GDC-0199/ABT-199) Versus Obinutuzumab and Chlorambucil in Previously Untreated Patients With CLL and Coexisting Medical Conditions.
13. Stenger M. 2019 ASCO: CLL14 Trial Evaluates First-Line Venetoclax/Obinutuzumab in Previously Untreated CLL. The ASCO Post. https://www.ascopost.com/News/60135. Updated June 12, 2019.
14. Fischer K, Al-sawaf O, Bahlo J, et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. N Engl J Med. 2019;380(23):2225-2236.
15. U.S Food & Drug Administration. FDA Warns about the risks associated with the investigational use of Venclexta in Multiple Myeloma. Available at www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-risks-associated-investigational-use-venclexta-multiple-myeloma. Updated March 21, 2019.
16. Wei AH et al., A phase 3 study of venetoclax plus low-dose cytarabine in previously untreated older patients with acute myeloid leukemia (viale-C): a 6-month update. Hemasphere, 2020, 4, 19-20; 25th Congress of European Hematological Association; conference abstract. Added 08/2020.
17. DiNardo CD, Jonas BA, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med. 2020 Aug 13;383(7):617-629.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated supporting evidence for venetoclax phase III confirmatory clinical trials for newly diagnosed acute myeloid leukemia (AML)	12/2020
Added new FDA approval in untreated CLL/SLL in combination with obinutuzumab (Gazyva)	06/2019
Added new FDA approval in Acute Myeloid Leukemia.	12/2018
Included new FDA expanded indication in CLL/SLL without 19p deletion and expanded initial approval to 6 months.	08/2018

Policy Type: PA Pharmacy Coverage Policy: UMP224

Description

Vericiguat (Verquvo) is an orally administered guanylate cyclase stimulator.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
vericiguat (Verquvo)	2.5 mg tablets	Reduce the risk of cardiovascular death and heart failure (HF) hospitalization following a hospitalization for HF or need for outpatient IV diuretics in adults with symptomatic chronic HF and ejection fraction less than 45%	30 tablets/30 days
	5 mg tablets		
	10 mg tablets		

Initial Evaluation

I. Vericiguat (Verquvo) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a cardiologist; **AND**
   C. A diagnosis of **chronic heart failure with reduced ejection fraction (HFrEF)** when the following are met:
      1. Member has HFrEF defined as New York Heart Association functional class II, III, or IV; **AND**
      2. Member has a documented reduced left ventricular ejection fraction of less than 45%; **AND**
      3. Provider attestation that member has recent evidence of worsening heart failure as defined by ONE of the following:
         i. Hospitalization for heart failure within the last six months; **OR**
         ii. Receiving intravenous (IV) diuretic therapy, within the last three months; **AND**
      4. Member is being treated with one agent from each of the following groups unless ineffective, contraindicated or not tolerated:
         i. Group 1: Beta-blocker (e.g., metoprolol succinate, carvedilol, bisoprolol)

ii. Group 2: ACE-I/ARB (e.g., lisinopril, losartan, valsartan, ramipril) OR ARNI (i.e. sacubitril/valsartan)
iii. Group 3: Mineralocorticoid antagonist (e.g., spironolactone)

II. Vericiguat (Verquvo) is considered investigational when used for all other conditions, including but not limited to:
A. Heart failure with preserved ejection fraction (HFpEF)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **OR**
IV. In the absence of improvement or stability of disease symptoms, the provider attests continuation of therapy is medically necessary AND clinical rationale of medical necessity has been provided and reviewed by a Moda Health clinician.

Supporting Evidence

I. Vericiguat (Verquvo) was studied in one randomized, double-blind, placebo-controlled Phase 3 (VICTORIA) trial in 5,050 patients with chronic heart failure (NYHA functional class II, III or IV) with a reduced ejection fraction (<45%), evidence of recent decompensation or worsening heart failure, defined as recent hospitalization for heart failure in the last three months, hospitalization in the last three to six months, or receiving intravenous (IV) diuretic therapy, without hospitalization, within the last six months.
II. The primary efficacy outcome was a composite endpoint of death from cardiovascular causes or first hospitalization for heart failure. The primary endpoint was achieved by 897 patients (35.5%) in the vericiguat group and 972 patients (38.5%) in the placebo group (hazard ratio, 0.90; 95% CI 0.82 to 0.98; P=0.02).
III. Adverse events occurred in 80.5% of patients receiving vericiguat (Verquvo) with serious adverse events occurring in 32.8% of those patients. Notable side effects observed during the clinical trial include symptomatic hypotension (9.1% patients in vericiguat group vs. 7.9% in placebo group) and syncope (4.0% patients in vericiguat group vs. 3.5% in placebo group). Anemia developed in 7.6% patients in the vericiguat group compared to 5.7% patients in the placebo group. Of those developing anemia, 1.6% cases in the vericiguat group and 0.9% in the placebo group were considered serious adverse events.
IV. The 2017 AHA/ACC/HFSA guidelines recommend first-line therapy with an ACE-I or ARB and a guideline directed beta blocker (bisoprolol, carvedilol or metoprolol succinate) with use of diuretics as needed for symptom management. Spironolactone, sacubitril/valsartan, isosorbide

dinitrate, hydralazine, and ivabradine can be used as adjunct therapy to first-line agents based on patients NYHA functional class and other specified patient characteristics. In the VICTORIA trial, 60% of patients received triple therapy with a beta blocker, ACE-I/ARB/ARNI, and mineralocorticoid antagonist in addition to the study drug.

V. Vericiguat (Verquvo) was studied in adult patients age 18 and older and has not been evaluated for safety and/or efficacy in pediatric patients.

Investigational or Not Medically Necessary Uses

I. Vericiguat (Verquvo) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Heart failure with preserved ejection fraction (HFpEF)
      i. Vericiguat (Verquvo) was studied in two phase 2b trials, SOCRATES-PRESERVED and VITALITY-HFpEF, in the setting of chronic heart failure with preserved ejection fraction. The primary efficacy endpoints of change in baseline in log-transformed N-terminal pro-B-type natriuretic peptide (NT-ProBNP) and left atrial volume (LAV) and change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) PLS quality index, respectively, were not met for either study and phase III studies were not pursued.

References

1. Armstrong P, et al. Vericiguat in patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2020; 382:1883-93. DOI: 10.1056/NEJMoa1915928
2. Yancy et al. 2017 ACC/AHA/HFSA Heart Failure Focused Update. JACC. 2017; 70(6):776-803.
3. Pieske B, et al. Vericiguat in patients with worsening chronic heart failure and preserved ejection fraction results of the Soluble guanylate Cyclase stimulator in heart failure patients with preserved EF (SOCRATES-PRESERVED) study. European Heart Journal (2017) 38, 1119-1127. Doi: 10.1093/eurheartj/ehw593
4. Armstrong P, et al. Effect of Vericiguat vs Placebo on Quality of Life in Patients with Heart Failure and Preserved Ejection Fraction: The VITALITY-HFpEF Randomized Clinical Trial. JAMA. 2020;324(15):1512-1521. DOI: 10.1001/JAMA.2020.15922.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP072

Description

Vigabatrin's (Sabril, Vigadrone) full mechanism of action is unknown at this time; however, it is an orally administered agent that has irreversible inhibition of gamma-aminobutyric acid transaminase (GABA-T).

Length of Authorization

- Initial: Three months for complex partial epileptic seizure, and one month for West Syndrome
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
vigabatrin (Sabril)	500mg tablets	Refractory complex partial epileptic seizure, adjunct therapy	180 tablets/30 days
vigabatrin (Sabril, Vigadrone)	500mg/packet powder for oral suspension		180 packets/30 days
		West Syndrome (infantile spasms)	120 packets/30 days

Initial Evaluation

I. Vigabatrin (Sabril, Vigadrone) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a neurologist; **AND**
   B. The member has had an ophthalmologic examination prior to initiating vigabatrin (Sabril) or will be examined no later than four weeks after initiation of therapy; **AND**
      1. The member will have an ophthalmologic examination at least every three months during treatment; **OR**
   C. The member is blind prior to initiation of therapy; **AND**
   D. Generic vigabatrin OR vigabatrin (Vigadrone) is prescribed, or documentation is provided regarding clinical rationale as to why generic vigabatrin or vigabatrin (Vigadrone) is not appropriate or is contraindicated; **AND**
   E. A diagnosis of one of the following:
      1. **Complex partial epileptic seizure (focal onset impaired awareness seizure)**; **AND**
         i. Vigabatrin (Sabril, Vigadrone) will be used in combination with at least one other anti-epileptic medication (i.e., used as adjunct therapy) such as

carbamazepine, phenytoin, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, divalproex sodium, zonisamide, tiagabine; **AND**

ii. A trial and failure of at least two anti-epileptic medications listed above; **AND**

iii. Member is two years of age or older; **OR**

2. **West Syndrome (Infantile Spasms)**; **AND**

i. Member is between one month and two years of age; **AND**

ii. The prescribed dose does not exceed 150 mg/kg/day

II. Vigabatrin (Sabril, Vigadrone) is considered investigational when used for all other conditions, including but not limited to:

A. Seizures that are not considered complex partial epileptic or focal onset impaired awareness seizures

B. Tourette's disorder

C. Substance abuse (e.g., cocaine, methamphetamine, alcohol dependence)

D. Autoimmune encephalitis

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Provider attestation that ophthalmologic examination has been completed every three months since initiation of therapy; **AND**

IV. Generic vigabatrin OR vigabatrin (Vigadrone) is prescribed, or documentation is provided, regarding clinical rationale as to why generic vigabatrin or vigabatrin (Vigadrone) is not appropriate or is contraindicated **AND**

V. A reduction in the severity or frequency of seizures or spasms; **AND**

A. **Complex partial epileptic seizure (focal onset impaired awareness seizure)**; **AND**

1. The medication continues to be used in combination with at least one other anti-epileptic medication (i.e., used as adjunct therapy) such as carbamazepine, phenytoin, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, divalproex sodium, zonisamide, tiagabine; **OR**

B. **West Syndrome (Infantile Spasms)**; **AND**

1. Clinical benefit has been assessed and documented within the first two to four weeks of treatment (please note: extensions will not be given if assessment has not taken place within four weeks of treatment initiation); **AND**

2. The prescribed dose does not exceed 150 mg/kg/day

Supporting Evidence

I. Vigabatrin (Sabril, Vigadrone) has a black box warning for permanent vision loss, and those who take the medication are at risk for vision loss with any amount of medication. The risk increases with greater doses and duration of vigabatrin (Sabril, Vigadrone) administration. This medication is available through a Risk Evaluation Mitigation Strategy (REMS) Program, and a specialist will need to be involved in prescribing to ascertain if the benefits of vigabatrin (Sabril, Vigadrone) outweigh the risk of vision loss.

II. Recommended ophthalmologic monitoring should start at baseline or within four weeks of initiating therapy, every three months during therapy, and through three to six months post discontinuation.

III. Vigabatrin (Sabril, Vigadrone) is FDA-approved for complex partial epileptic seizures (focal onset impaired awareness seizure) for ages two years and older and West Syndrome (infantile spasms) for ages one month to two years. In complex partial epileptic seizure, the medication is FDA-approved in the refractory setting after failure of other therapies and should be used in addition to at least one other anti-epileptic (i.e., vigabatrin [Sabril, Vigadrone] is an adjunct therapy).

IV. Vigabatrin (Vigadrone) is an AA-rated authorized generic of Sabril and is fully substitutable for both Sabril and generic vigabatrin 500mg/packet for oral solution.

V. The max dose of vigabatrin (Sabril, Vigadrone) is 3000 mg/day for complex partial epileptic seizure and a maximum of 150 mg/kg/day for West Syndrome.

VI. For West Syndrome, significant clinical benefit should be realized within four weeks of therapy initiation, and the medication should be discontinued if not. Due to the risks associated with the medication, continuation of therapy will not be grated in absence of clinical benefit.

Investigational or Not Medically Necessary Uses

All indications listed below have not been sufficiently studied for safety and efficacy or have inconclusive evidence for use of vigabatrin (Sabril, Vigadrone).

I. Seizures that are not considered complex partial epileptic or focal onset impaired awareness seizures

II. Tourette's disorder

III. Substance abuse (e.g., cocaine, methamphetamine, alcohol dependence)

IV. Autoimmune encephalitis

References

1. Sabril [Prescribing Information]. Deerfield, IL: Lundbeck. January 2020.
2. Vigadrone [Prescribing Information]. Maple Grove, MN: Upsher-Smith Laboratories, LLC. February 2020.
3. Approved Risk Evaluation and Mitigation Strategies (REMS). Food and Drug Administration. October, 2017. https://www.accessdata.fda.gov/Scripts/Cder/Rems/index.cfm?event=RemsDetails.page&REMS=364. Accessed March 4, 2019.
4. Vigabatrin Risk Evaluation and Mitigation Strategy (REMS) Program. Vigabatrin REMS for Healthcare Professionals. https://www.vigabatrinrems.com/#Main. Accessed March 4, 2019.
5. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58(4):512-521.
6. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2018;91(24):1117.

7. Dean C, Mosier M, Penry K. Dose-Response Study of Vigabatrin as add-on therapy in patients with uncontrolled complex partial seizures. *Epilepsia*. 1999;40(1):74-82.
8. Köhler U, Forberg J. [Results of treatment of 718 endometrial cancers with reference to clinical and morphologic prognostic factors]. *Zentralbl Gynakol*. 1989;111(15):1033-41.

Policy Implementation/Update:

Action and Summary of Changes	Date
• Updated minimum age for use as adjunct therapy for refractory complex seizures to age two and older to align with FDA-label age-expansion • Added Vigadrone packets to policy	03/2021
Date created	03/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP198

Split Fill Management*

Description

Vismodegib (Erivedge) is an orally administered hedgehog pathway inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
vismodegib (Erivedge)	150 mg capsules	Basal cell carcinoma; metastatic or locally advanced	28 capsules/28 days

Initial Evaluation

I. Vismodegib (Erivedge) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist or dermatologist; **AND**
   C. Vismodegib (Erivedge) will NOT be used in combination with any other oncologic medication; **AND**
   D. Member has not progressed on any other oncologic medication (e.g. has not progressed on sonidegib [Odomzo]); **AND**
   E. A diagnosis of **basal cell carcinoma (BCC)** when the following are met:
      1. Member has metastatic (Stage IV) basal cell carcinoma; **OR**
      2. Member has locally advanced basal cell carcinoma; **AND**
         i. Basal cell carcinoma has recurred or progressed after radiation or surgery; **OR**
         ii. Member is not a candidate for either

II. Vismodegib (Erivedge) is considered investigational when used for all other conditions, including but not limited to:
   A. Ovarian Cancer
   B. Nevoid basal cell carcinoma syndrome
   C. Prostate Cancer

D. Acute leukemia
E. Lymphoma
F. Breast Cancer
G. Medulloblastoma
H. Multiple myeloma
I. Myelofibrosis
J. Graft versus host disease
K. Pancreatic cancer
L. Lung cancer
M. Hepatocellular carcinoma

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Vismodegib (Erivedge) is prescribed by, or in consultation with, an oncologist or dermatologist; **AND**
IV. Member has a diagnosis of **metastatic or locally advanced basal cell carcinoma; AND**
V. Member has experienced a clinical response to therapy defined by improvement or stabilization of disease or decrease or stabilization of tumor size or spread; **AND**
VI. Provider attestation that the member, either male or female, has been counseled on the teratogenicity and embryo-fetal toxicity risks with vismodegib (Erivedge).

Supporting Evidence

I. The safety and efficacy of vismodegib (Erivedge) in basal-cell carcinoma was evaluated in the pivotal ERIVANCE trial; a multicenter, international, two-cohort, open-label, single-arm study of 104 patients with metastatic basal-cell carcinoma (BCC) and those with locally advanced BCC who had inoperable disease or who were not a candidate for surgery. Patients with locally advanced disease were required to have had prior radiation therapy, unless contraindicated or inappropriate.
II. The primary efficacy endpoint was the independently assessed objective response rate (ORR) based on RECIST guidelines for metastatic disease or a decrease of 30% or more in the externally visible or radiographic dimension or complete resolution of ulceration for locally advanced disease. The key secondary endpoint was duration of response (DOR). The study met its primary endpoint in both cohorts with an ORR of 30% (95% confidence interval [CI], 16 to 48; P=0.001) in the group with metastatic BCC and 43% (95% CI, 30 to 56; P<0.001) in the group with locally advanced BCC. The median duration of objective response was 7.6 months for metastatic BCC (rang, 2.1 to 11.1) and locally advanced BCC (range, 1.0 to 12.9).
III. During the ERIVANCE trial, all patients experienced at least one adverse event (AE), with the majority classified as grade 1 or 2 in severity, and 25% experienced at least one serious adverse

event. Of those who experienced a serious adverse event, seven patients experienced a fatal adverse event and 12% had an adverse event that led to discontinuation. Common adverse events included muscle spasms, dysgeusia, alopecia, fatigue and weight loss.

IV. Patients enrolled in the study were age 18 and older and concurrent antitumor (oncologic) therapy was not permitted. The safety and/or efficacy of use in pediatric and adolescent patients or in combination with other oncologic therapies has not been evaluated.

V. Vismodegib (Erivedge) carries a black box warning for Embryo-fetal toxicity, as this agent is known to cause embryo-fetal death or severe birth defects when administered to a pregnant woman. FDA-label advises women of reproductive potential and men to use effective contraception during therapy with vismodegib (Erivedge) and for 24 months after the final dose.

VI. Long-term safety and efficacy of vismodegib (Erivedge) was evaluated in a follow-up study of the ERIVANCE trial for 39 months after the final data cutoff date of the primary analysis. The primary end point was ORR, with key secondary endpoints including DOR and overall survival (OS). Of the 104 patients enrolled at baseline, 96 discontinued for the following reasons: disease progression (27.9%), patient decision to withdraw (26.0%), and AEs (21.9%). The ORR for the mBCC cohort was 48.5% [95% CI, 30.8-66.2] and 60.3% in the laBCC cohort [47.2-71.7]. Median DOR was 14.8 months for the mBCC cohort [7.4-16.6] with a median OS of 33.4 months; Median DOR was 26.2 months [9.0-37.6] and OS was not estimable.

VII. No new safety concerns arose during the follow-up study. Again, all patients enrolled in the study experienced one or more treatment emergent adverse events (TEAEs). The incidence of TEAEs increased between the time of the primary analysis and the final data cutoff date for the follow-up study and correlated with patients who had 12 or more months of exposure to vismodegib (Erivedge). Patients who received treatment for 12 months or more had higher rates of muscle spasms, alopecia, dysgeusia, weight decreased, fatigue, and nausea. Deaths occurring during the study were considered by the investigator to be related to vismodegib (Erivedge).

VIII. Vismodegib (Erivedge) is currently recommended by NCCN guidelines for use in recurrent or advanced disease, with the caveat to be used in the FDA-approved indication of metastatic or locally advanced disease, with a category 2A recommendation.

IX. Vismodegib (Erivedge) is FDA-approved for adults with metastatic and locally advanced basal cell carcinoma. Vismodegib (Erivedge) has an overlapping indication with sonidegib (Odomzo), and if disease progression has occurred on or after one of these therapies, there is currently insufficient evidence regarding safety and/or efficacy of the other. One published piece of literature evaluated sonidegib (Odomzo) in those that were resistant to vismodegib (Erivedge); however, this trial included only nine subjects all of which showed no response to sonidegib (Odomzo) or were not evaluable for safety and/or efficacy. Available evidence disfavors use of sequential Hedgehog pathway inhibitors.

Investigational or Not Medically Necessary Uses

I. Vismodegib (Erivedge) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Ovarian Cancer
   B. Nevoid basal cell carcinoma syndrome

C. Prostate Cancer
D. Acute leukemia
E. Lymphoma
F. Breast Cancer
G. Medulloblastoma
H. Multiple myeloma
I. Myelofibrosis
J. Graft versus host disease
K. Pancreatic cancer
L. Lung cancer
M. Hepatocellular carcinoma

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Vismodegib (Erivedge) [Prescribing Information]. Genentech USA, INC. South San Franicos, CA. January 2012.
2. Sekulic A, et al. Efficacy and Safety of Vismodegib in Advanced Basal-Cell Carcinoma. *N Engl J Med.* 2012 June 07; 366(23):2171-2179. Doi:10.1056/NEJMoal1113713.
3. Sekulic A, et al. Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma: final update of the pivotal ERIVANCE BCC study. *BMC Cancer* (2017) 17:332. Doi:10.1186/s 12885-017-3286-5/
4. National Comprehensive Cancer Network. NCCN Guidelines: Basal Cell Skin Cancer. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nmsc.pdf
5. Danial C., Sarin K. Oro A., et al. An investigator-initiated open-label trial of sonidegib in advanced basal cell carcinoma patients resistant to vismodegib. Clin Cancer Res. 2016;22: 1325-1329.

Policy Implementation/Update:

Action and Summary of Changes	Date
Transition to policy format, addition of supporting evidence, addition of requirement attesting agent will NOT be used in combination with any other oncologic medication, removal of teratogenicity counseling attestation.	10/2020
Previous review	01/2013 12/2012
Criteria created	07/2012

Policy Type: PA/SP Pharmacy Coverage Policy: UMP232

Split Fill Management*

Description

Voclosporin (Lupkynis) is an orally administered calcineurin-inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
voclosporin (Lupkynis)	7.9 mg capsules	Lupus Nephritis	180 capsules/30 days

Initial Evaluation

I. **Voclosporin (Lupkynis)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a rheumatologist or nephrologist; **AND**
   C. **Not** used in combination with biologic(s) [e.g., rituximab (Rituxan), abatacept (Orencia), belimumab (Benlysta)]; **AND**
   D. A confirmed positive autoantibody test [antinuclear (ANA) and/or anti-double-stranded DNA (anti-ds-DNA)]; **AND**
   E. A diagnosis of **Lupus Nephritis (LN); AND**
      1. Biopsy indicating class III (focal), IV (diffuse), or V (membranous) LN; **AND**
      2. Biopsy shows active lesions; **OR**
         i. Biopsy shows active AND chronic lesions; **AND**
      3. Provider attestation indicating medication will be given in combination with mycophenolate (CellCept) for induction and maintenance; **AND**
      4. Provider attestation the member will continue to receive standard therapy (e.g., antimalarials, NSAIDs, immunosuppressives, corticosteroids), unless all are contraindicated or not tolerated; **AND**
      5. Treatment with belimumab (Benlysta) has been ineffective, contraindicated, or not tolerated.

II. Voclosporin (Lupkynis) is considered investigational when used for all other conditions, including but not limited to:
   A. Systemic Lupus Erythematosus (SLE) with absence of lupus nephritis
   B. Severe active central nervous system lupus
   C. Renal transplantation

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. A diagnosis of **Lupus Nephritis (LN)**; **AND**
IV. Member has exhibited improvement or stability of disease symptoms (e.g., reduction in proteinuria, improved/stable serum creatinine, reduction in urinary sediment); **AND**
V. **Not** used in combination with other biologic(s) [e.g., rituximab (Rituxan), abatacept (Orencia), belimumab (Benlysta)]; **AND**
VI. Member will continue to receive standard therapy (e.g., antimalarials, NSAIDs, immunosuppressives, corticosteroids), unless all are contraindicated or not tolerated.

Supporting Evidence

I. LN is a kidney disease that develops in about 40% of patients with SLE. Approximately 10% of patients develop end stage renal disease (ESRD). Kidney failure, dialysis, and kidney transplants are common in this patient population. Patients with SLE with any sign of kidney involvement (glomerular hematuria and/or cellular casts, proteinuria >0.5 g/24 hours [or spot urine protein-to-creatine ratio (UPCR) >500 mg/g], unexplained decrease in glomerular filtration rate (GFR)) are candidates for kidney biopsy to confirm diagnosis/class of LN, which then guides treatment.
   - Class I (minimal mesangial) and Class II (mesangial proliferative): Usually does not need specific immunosuppressive therapy but may be prone to histological transformation to more aggressive disease on repeat biopsy.
   - Class III (focal) and Class IV (diffuse): active, chronic classifications at high risk of developing ESRD, thus are targeted populations for immunosuppressive therapies.
   - Class V (membranous): presents similar to nephrotic syndrome with subendothelial deposits. Patients with Class III or IV disease may have these deposits and can be classified as Class III or IV in combination with Class V, can also present as pure Class V. Immunosuppressive therapy is indicated.
   - Class VI (advanced sclerosing): patients with sclerosing lesions; generally, do not respond to immunosuppressive therapy; treatment requires dialysis and/or kidney transplant.

II. European Renal Association–European Dialysis and Transplant Association (EULAR/ERA–EDTA) 2019 and 2012 American College of Rheumatology guidelines on LN recommend immunosuppressive therapy for LN starting with an induction phase to achieve a renal response,

which is recommended for the first six months of treatment, followed by maintenance therapy. Initial (induction) treatment is recommended with mycophenolate mofetil (MMF) or low-dose intravenous cyclophosphamide, both combined with glucocorticoids (pulses of IV methylprednisolone, then oral prednisone). Subsequent long-term maintenance treatment with MMF or azathioprine should follow, with no, or low-dose (< 7.5 mg/day), glucocorticoids. If a patient fails to respond to the first six months of induction therapy, guidelines suggest switching the immunosuppressive agent in combination with glucocorticoid pulse. Alternatively, calcineurin inhibitors (tacrolimus or cyclosporine) can be used as monotherapy or in combination with MMF as induction/maintenance therapy particularly in refractory cases.

III. Guidelines recommend patients with LN be treated with hydroxychloroquine or an equivalent antimalarial, unless contraindicated, and adjunctive therapies be added to manage LN and attenuate complications of the disease.

IV. The safety and efficacy of voclosporin (Lupkynis) in pediatric patients has not been established.

V. The safety and efficacy of voclosporin (Lupkynis) in combination with biologic therapies [e.g., rituximab (Rituxan), abatacept (Orencia), belimumab (Benlysta)] has not been evaluated.

VI. Per the package insert, use of voclosporin (Lupkynis) is not recommend in patients with a baseline eGFR less than or equal to 45 mL/min/1.73m^2 unless the benefit exceeds the risk, as these patients may be at increased risk for acute and/or chronic nephrotoxicity.

VII. Policy is specific to list MMF as the induction/maintenance therapy due to potential safety concerns of additive toxic effects that may occur when co-administering voclosporin (Lupkynis) and cyclophosphamide. Per the package insert, use of voclosporin (Lupkynis) in combination with cyclophosphamide has not been established and is not recommended. The FDA review of voclosporin (Lupkynis) further adds “given the adverse reaction profile of cyclophosphamide and the lack of efficacy data for voclosporin in combination with cyclophosphamide, the review team concluded that there is reasonable concern about the benefit-risk profile in this situation, thus necessitating this limitation of use”.

VIII. Voclosporin (Lupkynis) was evaluated as an adjunct to standard therapy in a Phase 3, randomized, double-blind, placebo-controlled, 52-week trial in adults (n=357) with biopsy proven LN. The primary efficacy outcome was complete renal response at week 52, defined as a UPCR < 0.5, eGFR ≥ 60 ml/min per 1.73 m2 or a decline in no more than 20% from baseline, no rescue therapy, and a sustained dose ≤than 10 mg of prednisone. The primary endpoint was met with 73 patients (40.8%) in the voclosporin (Lupkynis) arm achieving renal response compared to 40 patients (22.5%) in the placebo arm (odds ratio 2.7; 95% CI: 1.6-4.3; P<0.001).

- All patients included in the trial were on background therapy with mycophenolate mofetil plus corticosteroids. Patients were 18 years of age and older with antibody positive SLE, ratio of urinary protein to creatinine (UPCR) of 2 or more (average patient had a baseline UPCR of 4), biopsy proven LN class III (focal lupus nephritis) or IV (diffuse lupus nephritis) with, or without, coexisting class V (membranous lupus nephritis), or pure class V lupus nephritis within last 6 months. All patients also had biopsy specimens showing active lesions or active and chronic lesions.

IX. As of date there are no head to head trials comparing voclosporin (Lupkynis) to belimumab (Benlysta). Additionally, guidelines do not have recommendations around preferring either agent in the setting of LN. However, given the potential for chronic calcineurin inhibitor-related nephrotoxicity, especially relevant to this patient population with underlying renal disease, and

the insufficient long-term controlled safety data beyond one year, the plan requires trial of or contraindication to belimumab (Benlysta) prior to use of voclosporin (Lupkynis).

Investigational or Not Medically Necessary Uses

I. Voclosporin (Lupkynis) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Systemic Lupus Erythematosus (SLE) in absence of lupus nephritis (LN)
   B. Severe active central nervous system lupus
   C. Renal Transplantation

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Lupkynis [Prescribing Information]. Aurinia Pharma U.S., Inc.: Rockville, MD. January 2021.
2. Almaani S, Meara A, Rovin BH. Update on lupus nephritis. Clin J Am Soc Nephrol. 2017;12(5):825-835.
3. Lim SS, Bayakly AR, Helmick CG, Gordon C, Easley KA, Drenkard C. The incidence and prevalence of systemic lupus erythematosus, 2002–2004: The Georgia Lupus Registry. Arthritis Rheumatol 2014;66:357–68.
4. 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.
5. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney inter., Suppl.2012;2: 139–27.
6. Fanouriakis A, Kostopoulou M, Cheema K, et al. 2019 update of the joint European league against rheumatism and European renal association-European dialysis and transplant association (Eular/era-edta) recommendations for the management of lupus nephritis. Ann Rheum Dis. 2020;79(6):713-723.
7. FDA Center for Drug Evaluation and Research. Application number: 213716Orig1s000. Multi-Discipline review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/213716Orig1s000MultidisciplineR.pdf

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP025

Description

Vonvendi is a recombinant von Willebrand factor indicated for use in adults diagnosed with von Willebrand disease for on-demand treatment and control of bleeding episodes, perioperative management, and routine prophylaxis in patients with severe Type 3 von Willebrand disease receiving on-demand therapy.

Length of Authorization

- Initial: 6 months (for on-demand and prophylaxis); 1 month (for perioperative)
- Renewal: 12 months

Quantity limits

Product Name	Indication/ FDA Labeled Dosing	Dosage Form	Quantity Limit
Vonvendi, von Willebrand factor (recombinant)	**On-demand treatment and control of bleeding episodes:** • *Minor:* Up to 50 IU/kg for the initial dose, subsequent doses of up to 50 IU/kg every eight to 24 hours as clinically required • *Major:* Up to 80 IU/kg for the initial dose, subsequent doses of up to 60 IU/kg every eight to 24 hours for approximately two to three days, as clinically required **Perioperative management of bleeding:** A dose may be given 12 to 24 hours prior to surgery to allow the endogenous factor VIII levels to increase to at least 30 IU/dL (minor surgery) or 60 IU/dL (major surgery) **Routine prophylaxis to reduce the frequency of bleeding episodes in patients with severe Type 3 VWD receiving on-demand therapy:** • For initiation, administer 40 to 60 IU/kg twice weekly • Adjust up to 60 IU/kg twice weekly if breakthrough bleeding occurs in joints or if severe bleeding occurs	650, 1300 IU	**On-demand treatment and control of bleeding episodes:** Up to the number of doses requested every 28 days **Perioperative management of bleeding:** Up to the number of doses requested every 28 days **Routine prophylaxis to reduce the frequency of bleeding episodes in patients with severe Type 3 VWD receiving on-demand therapy:** Up to the number of doses requested every 28 days

Initial Evaluation

I. **von Willebrand factor (Vonvendi)** may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by, or in consultation with, a hematologist; **AND**
   B. A diagnosis of von Willebrand disease (vWD) has been confirmed by blood coagulation and von Willebrand factor testing; **AND**
   C. Use is planned for one of the following indications:
      1. On-demand treatment and control of bleeding when one of the following is met:
         i. Member has severe von Willebrand disease (vWD); **OR**
         ii. Member has mild or moderate von Willebrand disease (vWD); **AND**
            a. The use of desmopressin is known or suspected to be ineffective or contraindicated; **OR**
      2. Perioperative management of bleeding; **OR**
      3. Routine prophylaxis and ALL are met:
         i. Confirmed severe type 3 VWD; **AND**
         ~~ii.~~ Currently receiving on-demand therapy.

II. Vonvendi is considered investigational when used for all other conditions.

Renewal Evaluation

I. Documentation of clinical benefit, including decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline

Supporting Evidence

I. Von Willebrand disease (vWD) is the most common of the inherited bleeding disorders. Although vWD is common, only a fraction of patients seeks out medical attention of bleeding symptoms due to the mild nature of the disease in many patients, and the lack of bleeding challenges.
II. There are three types of inherited vWD:
   - Type 1 – The most common type that accounts for about 70% of cases. It reflects a quantitative deficiency of von Willebrand factor (vWF). The clinical presentation varies from mild to moderately severe.
   - Type 2 – Accounts for 25-30% of cases and is characterized by several qualitative abnormalities of vWF (e.g. altered size rations or biologic properties).
   - Type 3 – The most severe type of disease with very low or undetectable levels of vWF. Patients typically present with severe bleeding involving both the skin and mucous membrane surfaces and soft tissues and joints. Replacement therapy with vWF is usually required.
III. Choice of therapy begins with an accurate and complete diagnosis of vWD, plus patient-specific factors must be taken to account (e.g. history of bleeding, response to prior therapies).
IV. A trial of desmopressin (DDAVP) should be considered in all patients with type 1 and most with type 2, but not in patients with type 3 vWD. Typically, minor bleeding episodes can be treated

with DDAVP without further therapeutic intervention. Major surgery typically requires replacement with vWF.

V. Patients with type 3 vWD, those with more severe type 1, and many of those with certain subtypes of type 2 disease often require replacement therapy with a vWF-containing product to control bleeding.

VI. The safety and efficacy of Vonvendi was established based on a series of 22 patients with vWD over the age of 18 years of age who experienced 192 bleeding episodes (mostly mucosal, seven major). Results showed the Vonvendi was highly effective in restoring hemostasis. Most episodes were treated with a single infusion.

VII. Use in routine prophylaxis was approved via a prospective, single arm, open-label, multicentered study that evaluated efficacy, safety, PK/PD of prophylactic treatment. Patients were age 18 years and older and diagnosed with vWD. Treatment groups included the prior on-demand (only received on-demand therapy) patients (n=13) and the switch (previously receiving prophylaxis therapy with plasma derived VWF (pdVWF)) patients (n=10). Treatment included rVWF 50 +/- 10 IU/kg twice weekly for the prior on-demand group and rVWF based on pdVWF weekly dose equivalent divided into 1-3 weekly infusions for the switch group for 12 months. Primary endpoint was the change in annualized bleeding rate (ABR) for spontaneous and non-traumatic bleeding events (BE) versus historical ABR.

VIII. The prior on-demand group had reduced ABR by 91.5% (mean ABR from 6.54 to 0.56) and the switch group had reduced ABR by 45% (mean ABR from 0.51 to 0.28) versus their historical ABR. No outstanding safety concerns noted outside of current data. Three serious AEs were reported that were considered unrelated to rVWF treatment (injuries due to a fall, 1 UTI, 1 related to rheumatoid arthritis comorbidity). There were no additional safety issues noted with the switch group. There were no binding or neutralizing antibodies found to either the rVWF or FVIII.

IX. Overall, the study demonstrated efficacy and safety for use of prophylaxis rVWF in patients who were only using on-demand therapy to reduce BEs. There was no significant efficacy for use in patients who were previously receiving other prophylactic therapy. However, given the rarity of this specific subtype and the lack of FDA-indicated products for prophylaxis use in this bleeding disorder, allowance in use of previously prophylaxis-treated patients provides access and other options in a limited treatment space.

Investigational or Not Medically Necessary Uses

There is no evidence to support the use of Vonvendi in any other condition.

References

1. Vonvendi® [Prescribing Information]. Westlake Village, CA: Baxalta US Inc; April 2022
2. National Hemophilia Foundation. MASAC Recommendations Concerning products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. Available from: https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations. Accessed July 5, 2019.
3. Nathan T. Connell, Veronica H. Flood, Romina Brignardello-Petersen, Rezan Abdul-Kadir, Alice Arapshian, Susie Couper, Jean M. Grow, Peter Kouides, Michael Laffan, Michelle Lavin, Frank W. G. Leebeek, Sarah H. O'Brien, Margareth C. Ozelo, Alberto Tosetto, Angela C. Weyand, Paula D. James, Mohamad A. Kalot, Nedaa Husainat, Reem A. Mustafa; ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. Blood Adv 2021; 5 (1): 301–325. doi: https://doi.org/10.1182/bloodadvances.2020003264

4. Leebeek FWG, Peyvandi F, Escobar M, Tiede A, Castaman G, Wang M, Wynn T, Baptista J, Wang Y, Zhang J, Mellgård B, Özen G. Recombinant von Willebrand factor prophylaxis in patients with severe von Willebrand disease: phase 3 study results. Blood. 2022 Jul 14;140(2):89-98. doi: 10.1182/blood.2021014810. PMID: 35439298; PMCID: PMC9283967.
5. UpToDate, Inc. Treatment of von Willebrand disease. UpToDate [database online]. Last updated November 29, 2022.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
Factor VIII/VWF Complex (Alphanate®, Humate-P®, Wilate®)	Control and prevention of bleeding – hemophilia A
	Perioperative management – hemophilia A
	Control and prevention of bleeding – vWD
	Perioperative management – vWD

Policy Implementation/Update:

Action and Summary of Changes	Date
Added new indication and supportive evidence for prophylaxis use in patients with severe Type 3 vWD who are receiving on-demand therapy. Added new renewal approval duration of 12 months for prophylaxis use. Added related policies section.	03/2023
New policy created for von Willebrand factor (Vonvendi)	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP217

Split Fill Management*

Description

Vorinostat (Zolinza) is an orally administered inhibitor of histone deacetylase (HDAC) enzymes (HDAC1, HDAC2, HDAC3 and HDAC6).

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
Vorinostat (Zolinza)	100 mg capsules	Cutaneous T-Cell Lymphoma	120 capsules/30 days

Initial Evaluation

I. Vorinostat (Zolinza) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist or a dermatologist; **AND**
   C. Medication will not be used in combination with any other oncolytic agent; **AND**
   D. Medication will not be used in combination with skin-directed therapies (e.g. Total Skin Electron Beam Therapy [TSEBT], phototherapy); **AND**
   E. Member has not progressed on, or after, prior treatment with HDAC inhibitor (e.g. romidepsin [Istodax]); **AND**
   F. A diagnosis of **cutaneous T-cell lymphoma (CTCL) [i.e. Sezary syndrome, mycosis fungoides]** when the following are met:
      1. Member has progressive (stage II or higher) or recurrent disease; **AND**
      2. Treatment with <u>two</u> or more of the following <u>systemic</u> regimens have been ineffective or not tolerated:
         i. Systemic retinoid (e.g. bexarotene [Targretin])
         ii. Methotrexate (oral or injectable)
         iii. Systemic chemotherapy (e.g. chlorambucil, cyclophosphamide, etoposide)
         iv. Targeted immunotherapy (e.g. mogamulizumab, brentuximab)
         v. Interferons (e.g. peginterferon-alfa 2b [PegIntron], interferon gamma [Actimmune])

II. Vorinostat (Zolinza) is considered investigational when used for all other conditions, including but not limited to:
   A. Malignant pleural mesothelioma
   B. Cutaneous B-cell lymphoma
   C. Multiple myeloma
   D. Hodgkin's lymphoma

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Medication is prescribed by, or in consultation with, an oncologist or a dermatologist; **AND**
III. Member has experienced response to treatment (e.g. complete or partial remission, decrease from baseline in SWAT skin assessment scores, or PGA scores)

Supporting Evidence

I. Vorinostat (Zolinza) is FDA-approved for the treatment of cutaneous manifestations in adult patients with cutaneous T-cell lymphoma (CTCL), who have progressive, persistent, or recurrent disease on, or following, 2 systemic therapies. Its approval was based on results from 2 single-arm, open-label trials. Efficacy and safety of vorinostat has not been studied in pediatric population.
II. Sézary syndrome (SS) and mycosis fungoides (MF) are the most common subtypes of advanced cutaneous T cell lymphoma (CTCL). MF is a mature T cell non-Hodgkin lymphoma with presentation in the skin, but lymph nodes, blood, and viscera may also be involved. Skin lesions include erythroderma, patches, plaques, or tumors that may be localized or widespread. SS is a distinctive erythrodermic CTCL with leukemic involvement of malignant T cells that typically match the clone in the skin; less frequently, distinct clones may be detected in skin and blood.
III. Advanced stage MF and SS are most often chronic with a persistent or relapsing course. The choice of therapy at different time points in the disease is largely dependent on the goals of therapy, which include long-term disease control and prompt symptom relief. Therefore, management of advanced and recurrent CTCL is often orchestrated by a multidisciplinary team comprised of dermatologists, medical oncologists, and radiation oncologists.
IV. Patients with early stage CTCL are treated with skin-directed therapies. A randomized trial demonstrated that early aggressive therapy with combination chemotherapy plus total skin electron beam radiation therapy (TSEBT) does not appear to improve survival when compared with the use of sequential topical regimens. Skin directed therapies include topical corticosteroids, topical chemotherapy (nitrogen mustard or carmustine), retinoids, imiquimod, and phototherapy (UVB or PUVA). There is no standard initial therapy, and experts differ in their preferred approach. Alternatively, for patients with generalized tumors (e.g., >10 percent body surface area), equally acceptable treatment options are the use of total skin electron beam therapy (TSEBT) and systemic therapies. TSEBT often provides a complete response (CR), albeit temporary in most cases, while systemic agents generally provide partial responses but can be given in a maintenance fashion. A choice among these treatments is made based on patient preference and clinician experience. Despite decades of experience in the treatment of SS and

MF, well-designed, prospective, controlled clinical studies comparing the efficacy of various therapies are lacking.

V. NCCN guideline for the treatment of recurrent or advanced CTCL (MF and SS) includes vorinostat (Zolinza) as one of the preferred regimens (category 2A recommendation). Systemic therapies in this space generally involve use of single agents. Multiagent chemotherapy regimens are reserved for patients, who have progressed after multiple agents in the preferred regiments (e.g. bexarotene, brentuximab, interferons, methotrexate, mogamulizumab, romidepsin). Participants in the clinical trials for vorinostat (Zolinza) did not have a history of prior treatment with an HDAC inhibitor. Efficacy and safety of vorinostat (Zolinza) after progression on another HDAC inhibitor (e.g. romidepsin) has not been studied. Additionally, Safety of combining TSEBT and phototherapy with vorinostat (Zolinza) is unknown. NCCN guideline for primary T-Cell lymphoma recommend against such combination regimen.

VI. In an open-label, single-arm, multicenter, nonrandomized clinical trial (N= 74), patients (median age 61 years) with advanced refractory CTCL were treated with vorinostat (400 mg daily). An objective clinical response of 30% was reported with median duration of response 4 weeks. The majority of patients (82.4%) had stage IIB and higher CTCL and had previously failed a median of 3 prior systemic therapies (range, 1 to 12). The primary efficacy endpoint was measured as either a complete clinical response or partial response (i.e. ≥ 50% decrease in a modified severity weighted assessment tool (SWAT) score from baseline) ORR was 29.7% (n= 22) (95% CI; 19.7, 41.5) The median times to response for the overall population and individuals with stage IIB and higher CTCL was 55 days and 56 days (range, 28 to 171 days), respectively. The median time to tumor progression (50% increase in the SWAT score from the nadir) was 202 days. Response to previous systemic therapy was not a response predictor to vorinostat.

VII. In a phase 2, open-label, single-center, nonrandomized trial (n=33, median age 67 years), vorinostat exhibited treatment response among previously-treated patients with relapsed or refractory CTCL. The majority (85%) patients had stage IIB and higher CTCL, and were refractory to, or intolerant to, prior systemic therapies (median, 5; range, 1 to 15). Patients were assigned to one of the 3 groups: group 1: vorinostat 400 mg daily (n=13); group 2: vorinostat 300 mg twice daily for 3 days with 4 days rest (n=11) and group 3: vorinostat 300 mg twice daily for 14 days with 7 days rest, followed by 200 mg twice daily (n=9). Oral retinoids, vitamin A or alternative medicines were not allowed. Physician's global assessment (PGA) scores were used for assessing improvement/ partial response. Based on the intent-to-treat analysis, the ORR were 31%, 9%, and 33% in groups 1, 2, and 3, respectively. The ORR was 24.2% (n= 8) in the overall population, 25% (n= 7) in individuals with stage IIB or higher disease, and 36.4% (n= 4) in patients with Sezary syndrome.

VIII. During clinical trials, participants receiving vorinostat (Zolinza) reported significant adverse reactions and drug toxicity events. Fatigue (73%), thrombocytopenia (54%), diarrhea (49%), nausea (49%), and dysgeusia (46%) were the most common adverse drug reactions leading to dose reductions. Overall, 19% participants discontinued treatment due to adverse reactions. Vorinostat has been included in the Institute for Safe Medication Practices (ISMP) list of drug classes, which have a heightened risk of causing significant patient harm when used in error.

Investigational or Not Medically Necessary Uses

I. There is insufficient evidence to support the use of vorinostat (Zolinza) for conditions other than cutaneous T-cell lymphoma.
   A. Malignant pleural mesothelioma: Vorinostat (Zolinza) showed some evidence of efficacy in an initial phase I study. However, extensive evaluation did not confirm a clinically meaningful benefit from this approach. In a phase III trial, 661 previously treated patients were randomly assigned to either vorinostat or placebo. Progression free survival (PFS) was prolonged with vorinostat (median, 6.3 weeks versus 6.1 weeks; hazard ratio [HR] 0.75, 95% CI 0.63-0.88). However, this increase was not clinically significant. Also, the difference in overall survival was not significant (median, 30.7 weeks versus 27.1 weeks; HR 0.98, 95% CI 0.83-1.17).

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Vorinostat (Zolinza)prescribing information. Whitehouse Station, NJ: Merck & Co, Inc; December 2018.
2. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Primary cutaneous lymphomas. 1.2021. October 12, 2020; National Comprehensive Cancer Network. Available from: https://www.nccn.org/professionals/physician_gls/pdf/primary_cutaneous.pdf
3. Duvic M, Talpur R, Ni X, et al: Phase II trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood 2007; 109(1):31-39.
4. Olsen EA, Kim YH, Kuzel TM, Pacheco TR, Foss FM, Parker S, Frankel SR, Chen C, Ricker JL, Arduino JM, Duvic M. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol. 2007 Jul 20;25(21):3109-15.
5. Krug LM, Kindler HL, Calvert H, et al. Vorinostat in patients with advanced malignant pleural mesothelioma who have progressed on previous chemotherapy (VANTAGE-014): a phase 3, double-blind, randomised, placebo-controlled trial. Lancet Oncol. 2015 Apr;16(4):447-56.

Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria transitioned to policy format. Added criteria noting combination of Zolinza with other oncolytic drugs and skin-directed therapies not allowed; Added requirement of member not having progressed on HDAC inhibitors; updated detailed requirements for failure of two systemic regimens with drug classes (based on NCCN guideline and clinical data); Added investigational uses and supporting evidence section to support the intent of this PA policy	01/2021
Criteria reviews and updates	09/2012; 12/2012; 01/2013
Criteria created	03/2012

Policy Type: PA/SP Pharmacy Coverage Policy: UMP248

Description

Vosoritide (Voxzogo) is a daily subcutaneously administered C type natriuretic peptide.

Length of Authorization

- Initial: Six months
- Renewal: Six months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
vosoritide (Voxzogo)	0.4 mg vials	To increase linear growth, in pediatric patients with achondroplasia	30 vials/30 days
	0.56 mg vials		
	1.2 mg vials		

Initial Evaluation

I. **Vosoritide (Voxzogo)** may be considered medically necessary when the following criteria are met:
   A. Member is one month or older; **AND**
   B. Member weighs 3kg or more; **AND**
   C. Medication is prescribed by, or in consultation with, a pediatric specialist in one of the following areas: neurology, orthopedic surgery, endocrinology, genetics; **AND**
   D. A diagnosis of **achondroplasia**; **AND**
      1. Provider attestation to the following:
         i. Genetic testing has been done to confirm diagnosis; **AND**
         ii. Epiphyses are open, as confirmed by radiographic imaging completed in the previous three months; **AND**
         iii. Member will not receive growth hormone treatment (e.g., Genotropin, Norditropin) concurrently with vosoritide (Voxzogo); **AND**
         iv. Limb lengthening surgery has not been performed in the past 18 months; **AND**
         v. At the time of vosoritide (Voxzogo) request, limb lengthening surgery is not planned to occur prior to closure of the epiphyses; **AND**

II. Vosoritide (Voxzogo) is considered investigational when used for all other conditions, including but not limited to:
   A. Forms of dwarfism other than achondroplasia
   B. For growth in patients with achondroplasia when epiphyses are closed
   C. Combination therapy with growth hormone treatment or limb-lengthening surgery

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Provider attestation to the following:
    A. If the member is 12 years of age or older or if epiphyses could be closed (e.g., precocious puberty, no height gained in previous few months): radiographic imaging on long bones has been completed within the past year to confirm epiphyses remain open (i.e., potential for growth still remains); **AND**
    B. Member will not receive growth hormone treatment (e.g., Genotropin, Norditropin) concurrently with vosoritide (Voxzogo); **AND**
    C. Limb lengthening surgery has not been performed in the past 18 months; **AND**
    D. At the time of vosoritide (Voxzogo) request, limb lengthening surgery is not planned to occur prior to closure of the epiphyses; **AND**
IV. Provider attestation that the most recent annualized growth velocity (AGV) is greater than the baseline AGV

Supporting Evidence

I. Vosoritide (Voxzogo), is FDA-approved to increase linear growth in pediatric patients with achondroplasia. It is a daily subcutaneous (SC) injection with dose based on patient body weight. In 2023, it was evaluated for safety and efficacy in patients at least one month of age and older, receiving FDA-approval in this age group. This expands the original label of those five and older with achondroplasia.
II. Achondroplasia is a condition of disproportionate short stature and affects 1:20,000 births. Gene mutations permanently activate the FGFR3 receptors, inhibit chondrocyte proliferation, and impair bone formation. Vosoritide (Voxzogo) is the first pharmacotherapy FDA-approved for this condition. There are no formal U.S. guidelines for the treatment of achondroplasia; however, management is highly specialized. Thus, a specialist prescriber is required.
III. Achondroplasia is caused by variants in the FGFR3 gene, and is recognized on genetic testing. Vosoritide (Voxzogo) targets the root cause of the condition, and safety and efficacy in other causes of forms of dwarfism are unknown, and is not expected to increase linear growth in other conditions. To rule out other causes or forms of dwarfism, genetic testing is required.
IV. Outside of lifestyle management (e.g., adaptation of home and school environments) and adjunctive care (e.g., treatment for sleep apnea), limb lengthening surgery may be considered. Surgery may be performed at any time, prior to or after epiphyses (i.e., growth plate) close. Evidence suggests there is greater success with surgery after epiphyses have closed. Therapy has not been evaluated for safety and efficacy in those that have received limb lengthening surgery within the past 18 months, or in conjunction with limb lengthening surgery. If surgery has been completed, vosoritide (Voxzogo) therapy should not be used within an 18-month window of surgery, to realize the benefits of surgical intervention. Furthermore, safety and efficacy of this therapy in conjunction with or to prepare for surgery has not been evaluated. Additionally, it is unknown if use of vosoritide (Voxzogo) will have additive effects if used prior to surgery; thus, if

surgery is planned or expected prior to final height being reached (e.g., closed epiphyses), therapy should be discontinued.

V. Vosoritide (Voxzogo) is not expected to provide further linear growth after epiphyses close. FDA and manufacturer guidance indicate that if epiphyses close, therapy should be discontinued at this time. Additionally, therapy should not be initiated in patients that have epiphysial closure. Routine imaging should be completed to evaluate medical necessity for therapy, and is required for initiation of therapy, as well as for renewal evaluation in patients of 12 years of age and older given the greater potential of epiphysial closure at in adolescence.

VI. Growth hormone therapy is controversial in patients with achondroplasia. It is not commonly used in the U.S. as evidence suggests this may exacerbate the disproportionate stature; however, evidence is conflicting. Dual therapy has not been evaluated for safety or efficacy; thus, concurrent use is not allowed.

VII. Vosoritide (Voxzogo) was evaluated in a Phase 3, randomized, blinded, placebo-controlled trial in 121 patients that were at least five years of age. Baseline AGV was around 4 cm/year for all patients. The primary outcome was an increase in annualized growth velocity (AGV) over baseline, which was statistically significant for vosoritide (Voxzogo) over placebo with an increase in AGV of 1.71 cm/year, compared to 0.13 cm/year. Therapy was also evaluated in a one-year, open-label extension trial where patients could continue therapy, and those originally randomized to placebo were switched to vosoritide (Voxzogo). The crossover group achieved an AGV of 1.62 cm/year, further supporting the pivotal trial results that therapy may influence an increase a 1.5-1.6 cm increase in AGV. Vosoritide (Voxzogo) has not yet shown to improve other disease manifestations, function, QoL, or reduction surgical intervention need. Vosoritide (Voxzogo) was granted Priority Review, Accelerated Approval, and Orphan Drug Designations. There will be a long-term, open-label trial to evaluate the drug's impact on final height. To assess if there has been an increase in AGV for patients on vosoritide (Voxzogo) therapy, a recently measured baseline AGV is required prior to initiation, as well as upon each renewal to determine if there is a continued treatment effect. In absence of continued treatment effect, continuation of therapy is not warranted at this time.

VIII. In 2023, vosoritide (Voxzogo) received approval by the FDA for an age expansion into those one month of age and older. This approval was based on a 52-week, phase 2, double-blind, placebo-controlled trial (Study 111-206) which evaluated the safety and efficacy in children with achondroplasia 0-60 months of age. There was a total of 75 patients, 43 received vosoritide and 32 placebo; patients were enrolled over three cohorts which assessed two different doses. Primary endpoints assessed the safety and tolerability, as well as the change from baseline in length/height Z-score. The change from baseline in AGV was measured as a secondary endpoint. Vosoritide (Voxzogo) was well tolerated with a safety profile consistent with those patients over five years of age. All patients had one adverse event with the most common being injection pain pain/redness. Over all patients in the 52-week period, there was an improvement of over 0.3 standard deviations (95% CI 0.07, 0.54) in height Z-score with vosoritide (n=43) versus placebo (n=32). This change was consistent with those children over five in the pivotal trial and across the three cohorts. Additionally, there was an increase in AGV of 0.92cm/year (95% CI 0.24, 1.59) with vosoritide compared to placebo. Vosoritide (Voxzogo) is weight based; thus, a recent weight from growing pediatric patients is required for initial and renewal coverage considerations for appropriate dose calculation. There is no data or experience in treating those under 3 kilograms.

Investigational or Not Medically Necessary Uses

I. Vosoritide (Voxzogo) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Forms of dwarfism other than achondroplasia. Vosoritide (Voxzogo) counteracts the genetic mutation that causes achondroplasia. In addition to lack of evidence for safety and efficacy, there is no expectation that therapy would be effective for other conditions, including other forms of dwarfism or short stature (e.g., growth hormone deficiency, Turner syndrome).
   B. For growth in patients with achondroplasia when epiphyses are closed
   C. Combination therapy with growth hormone treatment or limb-lengthening surgery

References

1. Voxzogo [Prescribing Information]. BioMarin Pharmaceutical Inc., Novato, CA. December 2021. Revised October 2023.
2. Savarirayan R, Tofts L, Irving M, et al. Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial. Lancet. 2020;396(10252):684-692.
3. Randel A. Aap guidelines on health supervision of patients with achondroplasia. AFP. 2006;73(6):1112.
4. Coste J, et al. Height and health-related quality of life: a nationwide population study. J Clin Endocrinol Metab. 2012;97(9):3231–3239.
5. Vosoritide product dossier. BioMarin. November 30, 2023.

Policy Implementation/Update:

Action and Summary of Changes	Date
Update to the policy and supporting evidence to include age expansion in those one month and older; removed requirement of documentation of current AGV and weight on initial and renewal	02/2024
Policy created	02/2022

Policy Type: PA/SP Pharmacy Coverage Policy: UMP171

Split Fill Management*

Description

Voxelotor (Oxbryta) is an orally administered hemoglobin S (HbS) polymerization inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit	
voxelotor (Oxbryta)	Sickle Cell Disease	500 mg tablets	90 tablets/30 days	
		300 mg soluble tablet	10 - <20 kg	60 tablets/30 days
			20 - <40 kg	90 tablets/30 days
			≥40 kg	150 tablets/30 days
		300 mg tablet	90 tablets/30 days	

Initial Evaluation

I. **Voxelotor (Oxbryta)** may be considered medically necessary when the following criteria are met:
   A. Member is 4 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a hematologist; **AND**
   C. Medication will not be used in combination with crizanlizumab-tmca (Adakveo); **AND**
   D. A diagnosis of **sickle cell disease (SCD)** when the following are met:
      1. Baseline hemoglobin level is ≤ 10.5 g/dL; **AND**
      2. Treatment with both the following have been ineffective, contraindicated, or both are not tolerated:
         i. Hydroxyurea (generic, Siklos, Droxia) for a minimum duration of six months; **AND**
         ii. L-glutamine (available over-the-counter); **AND**
      3. If requesting soluble tablets, member must demonstrate a medical reason they are unable to utilize oral tablets (e.g., weight, difficulty swallowing, oral/motor difficulties, feeding tube administration). Convenience of administration route does not equate to medical necessity

II. Voxelotor (Oxbryta) is considered investigational when used for all other conditions, AND when used in combination with crizanlizumab-tmca (Adakveo).

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy established through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Use of voxelotor (Oxbryta) is **not** in combination with crizanlizumab-tmca (Adakveo); **AND**
IV. Member has exhibited improvement or stability of disease symptoms (e.g., reduced vaso-occlusive crises (VOCs) compared to baseline, increase in hemoglobin levels, maintained increased hemoglobin levels); **AND**
V. If requesting soluble tablets, the member must demonstrate a medical reason they are unable to utilize oral tablets (e.g., weight, difficulty swallowing, oral/motor difficulties, feeding tube administration)

Supporting Evidence

I. Approval for voxelotor (Oxbryta) occurred following the phase 3 pivotal HOPE trial (Hemoglobin Oxygen Affinity Modulation to Inhibit HbS Polymerization). Subjects were between 12 to 65 years of age with confirmed sickle cell disease with documentation of one to 10 vaso-occlusive events within the past 12 months and baseline hemoglobin levels between 5.5 and 10.5 g/dL. Efficacy was based on hemoglobin response rate defined as a hemoglobin increase of >1 g/dL from baseline. The trial reported a response rate of 51.1% (46/90) compared to 6.5% (6/92) in the placebo group ($p < 0.001$).
II. The efficacy in younger pediatric patients was evaluated in the single arm, open label, HOPE-KIDS 1 trial which included patients aged 4 to <12 years old. Patients in the HOPE-KIDS 1 trial had a baseline hemoglobin ≤10.5 g/dL and 80% were on background hydroxyurea therapy. Previous vaso-occlusive event was not required. Similar to the HOPE trial, the primary outcome in HOPE-KIDS 1 was hemoglobin response rate, which was reported as 36% (16/45) (95% CI: 21.6%, 49.5%).
III. Voxelotor (Oxbryta) was approved under accelerated approval based on increase in hemoglobin. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial. There are no data to support an increase in hemoglobin level results in a reduction in vaso-occlusive events, or other complications related to sickle cell disease. Hemoglobin represents one of many factors contributing to vaso-occlusive events. Voxelotor (Oxbryta) approval was based on increase in hemoglobin and all patients included in trials had hemoglobin levels ≤10.5 g/dL, clinical necessity of voxelotor (Oxbryta) in patients with hemoglobin levels >10.5 g/dL is unknown. Per the American Society of Hematology (ASH), for patients with sickle cell disease receiving simple transfusions, the point of diminishing benefit of arterial oxygen delivery is estimated to be between 10 and 11 g/dL; beyond this point any increase in hemoglobin concentration decreases the arterial oxygen delivery.
IV. Acute complications and symptoms occur intermittently in sickle cell disease and throughout its course. These complications include vaso-occlusive pain crises (VOCs), acute chest syndrome, aplastic crisis, hemolytic crisis, and the pooling of blood within bodily organs. Vaso-occlusive

crises (VOCs) include stroke, severe pain, kidney and other organ and/or tissue damage for which there is no other explanation than vaso-occlusive crisis. Transfusion protocol is considered the most effective therapy for secondary stroke prophylaxis. If this is contraindicated or ineffective, hydroxyurea is introduced.

V. Hydroxyurea: Generic hydroxyurea is considered first-line in the treatment of sickle cell disease. Typically offered to patients with three or greater sickle cell-associated moderate-to-severe crises within the last 12 months. Has been shown to be disease modifying at reducing the rate of pain episodes, stroke, transfusion requirement, and mortality. Has been shown to reduce the number of VOCs and hospitalizations. The majority of subjects in the HOPE and HOPE-KIDS 1 trials were established on hydroxyurea at baseline.

VI. L-glutamine: Typically considered in patients who have at least two VOCs per year, despite maximally tolerated hydroxyurea dose, and considered against cost. Was approved to reduce acute complications of sickle cell disease (VOCs). Monotherapy is considered in patients who do not tolerate hydroxyurea. Over-the-counter products are available as well as in a prescription product L-glutamine (Endari)

VII. Both hydroxyurea and L-glutamine have evidence to support disease-modifying activity and the reduction of VOC or complications related to disease.

VIII. In children 12 years and older, as well as in adults, voxelotor (Oxbryta) is dosed as 1,500 mg daily. Children ages 4 to less than 12 years old follow weight-based dosing as noted in the table below.

Dosing in Children 4 to <12 years old:	
Weight	**Dose**
10 – 19 kg	600 mg once daily
20 – 39 kg	900 mg once daily
≥40 kg*	1,500 mg once daily

*Medical necessity for 300 mg soluble tablets is required for members weighing 40 kg or greater; as the recommended dose (1,500 mg daily) can be obtained with the 500 mg oral tablet, providing a significant price differential (~2.5x difference).

Investigational or Not Medically Necessary Uses

I. There is currently limited to no data to support the safety and efficacy of concomitant use of voxelotor (Oxbryta) with crizanlizumab-tmca (Adakveo).

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Oxbryta [Package Insert]. Global Blood Therapeutics. San Francisco, CA. December, 2021
2. Vichinsky E, Hoppe CC, Ataga KI et al. A phase 3 randomize trial of voxelotor in sickle cell disease. N Engl J Med. 2019; 381: 509-19.
3. Buchanan GR, Yawn BP, Afenyi-Annan AN et al. Evidence-based management of sickle cell disease: expert panel report. National Heart, Lung, and Blood Institute. 2014.
4. Center for Drug Evaluation and Research. Application Number 213137Orig1s000 Summary Review. Summary Review for Regulatory Action: NDA213137. Updated November 25, 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/213137Orig1s000Multidiscipline.pdf
5. Estepp JH, Kalpatthi R, Woods G, et al. Safety and efficacy of voxelotor in pediatric patients with sickle cell disease aged 4 to 11 years. Pediatr Blood Cancer. 2022;69(8):e29716.
6. Howard J, Ataga KI, Brown RC, et al. Voxelotor in adolescents and adults with sickle cell disease (Hope): long-term follow-up results of an international, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Haematol. 2021;8(5):e323-e333.
7. DeBaun MR, Jordan LC, King AA, et al. American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. Blood Advances. 2020;4(8):1554-1588.

Policy Implementation/Update:

Action and Summary of Changes	Date
Adding the 300mg non soluble tablet formulation to policy	01/2023
Updated member age requirement to 4 years of age and older. Removal of prior VOC requirement. Added requirement of baseline Hb ≤ 10.5 g/dL. Addition of medical necessity requirement for use of 300 mg soluble tablets over 500 mg tablet.	08/2022
Policy created	02/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP171

Split Fill Management*

Description

Zanubrutinib (Brukinsa) is an orally administered Bruton's Tyrosine Kinase (BTK) inhibitor.

Length of Authorization

- Initial: Six months (first three months split fill)
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
zanubrutinib (Brukinsa)	Mantle cell lymphoma in adults who have received at least one prior therapy	80 mg capsule	120 capsules/30 days
	Waldenström's macroglobulinemia in adults		
	Chronic lymphocytic leukemia or small lymphocytic lymphoma in adults		
	Relapsed or refractory marginal zone lymphoma in adults who have received at least one anti-CD20-based regimen		

Initial Evaluation

I. **Zanubrutinib (Brukinsa)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist, or hematologist; **AND**
   C. Medication will not be used in combination with any other oncolytic medication; **AND**
   D. Member has not previously progressed on a BTK inhibitor [e.g., ibrutinib (Imbruvica), acalabrutinib (Calquence)]; **AND**
   E. A diagnosis of one of the following:
      1. **Waldenström's Macroglobulinemia (WM)**; **AND**
         i. Member has received one prior therapy [e.g., chemotherapy, rituximab (Rituxan)]; **OR**
         ii. Provider attestation that member is not a candidate for standard immunochemotherapy based on documented risk factors or comorbidities

2. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL); AND

i. Medication is used in previously untreated CLL/SLL; **AND**

a. The member does not have a del17p mutation; **OR**

ii. Medication is used in the relapsed/refractory CLL/SLL; **AND**

a. Member has received one prior therapy [e.g., chemotherapy, venetoclax (Venclexta), obinutuzumab (Gazyva)]

II. Zanubrutinib (Brukinsa) is considered investigational when used for all other conditions, including but not limited to:

A. Previously untreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma in patients with a del17p mutation
B. Diffuse Large B-cell Lymphoma (DLBCL)
C. Follicular Lymphoma (FL)
D. Hairy Cell Leukemia (HCL)
E. Graft-versus Host Disease (GvHD)
F. Marginal Zone Lymphoma (MZL)
G. Indolent Non-Hodgkin Lymphoma (iNHL)
H. MCL monotherapy
I. MCL first-line therapy
J. MCL combination therapy
K. Richter's Transformation

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (e.g., no signs of disease progression); **AND**
IV. Zanubrutinib (Brukinsa) will not be used in combination with any other oncolytic medication

Supporting Evidence

I. **WM:**

A. Zanubrutinib (Brukinsa) is FDA-approved for WM based on the non-comparative assessment of DOR from zanubrutinib (Brukinsa) treatment arms and was granted Fast Track and Orphan Drug designation.
B. Zanubrutinib (Brukinsa) was studied in one Phase 1/2 open-label, dose expansion, single-arm trial of B-cell malignancies (BGB-3111-AU-003) in 77 WM patients and one head-to-head trial against ibrutinib (ASPEN). ASPEN was a Phase 3, randomized, active control, open-label trial which enrolled 137 relapsed/refractory (RR) and 37 treatment naïve WM adult patients. Median number of previously tried therapies included 1 (range: 1-8) and

majority (90%) were refractory to anti-CD20 therapies (rituximab, ofatumumab), alkylating agents (88%) (cyclophosphamide, chlorambucil, bendamustine), and glucocorticoids (72%). Treatment naïve patients consisted of those unsuitable for standard immunochemotherapy based on presence of comorbidities or risk factors precluding its use (e.g., age, cardiac, renal, infection comorbidities). Median patient age was 70 years of age. The trial excluded patients with previous exposure to BTK inhibitor therapy and those with WM central nervous system involvement. The primary endpoint of proportion of patients achieving very good partial response (VGPR) or CR was not reached. The trial efficacy analysis used hierarchical sequence; thus, all secondary endpoints were considered exploratory. Secondary endpoint of median PFS was not estimable, but 18-month PFS was 85% for zanubrutinib (Brukinsa) and 84% for ibrutinib. Median OS was not estimable at the time of analysis, but 18-month OS was 97% for zanubrutinib (Brukinsa) and 93% for ibrutinib.

C. Zanubrutinib (Brukinsa) had lower rates of atrial fibrillation (2% vs 15%), hypertension (11% vs 16%), minor bleeding (48.5% vs 59.2%), major hemorrhage (5.9% vs 9.2%), and diarrhea (20.8% vs 31.6%) compared to ibrutinib, respectively. The rate of neutropenia was 29.7% and 13.3% for zanubrutinib (Brukinsa) and ibrutinib, respectively.

D. NCCN guidelines recommend the following preferred therapies for the treatment of primary, and previously treated, WM: bendamustine/rituximab, bortezomib/dexamethasone/rituximab, ibrutinib $\pm$ rituximab (category 1), rituximab/cyclophosphamide/dexamethasone, and zanubrutinib (Brukinsa) (category 1).

II. **CLL/SLL:**

A. Efficacy and safety of zanubrutinib (Brukinsa) in treatment naïve CLL/SLL without a del17p mutation is established based on one Phase 3, open-label, randomized, active-controlled (cohort 1) trial (SEQUOIA). Enrolled patients (N=590) had untreated CLL/SLL, were ≥65 years of age or ≥18 years of age with comorbidities and were considered unsuitable for fludarabine-cyclophosphamide-rituximab treatment (defined as 65 years or older, a Cumulative Illness Rating Scale [CIRS] score of more than 6, creatinine clearance less than 70 mL/min, or history of severe or frequent infections). Patients in cohort 1 were without del17p mutation and were randomized 1:1 to zanubrutinib (Brukinsa) 160mg BID or bendamustine and rituximab (BR). Patients in cohort 2 (single-arm, open label portion of trial) had del17p mutation and underwent treatment with zanubrutinib (Brukinsa) by itself. As of December 2022, results are available for a median follow-up of 26.2 months. Median PFS and OS were not reached in any treatment group. Estimated PFS at 24 months was statistically superior for zanubrutinib (Brukinsa) as compared to BR (85.5% vs 69.5%) p<0.001. In cohort 1, the difference in PFS between the treatment groups was not significant among patients with mutated IGHV, small subgroup of patients with SLL, and those with pathogenic TP53 mutation. Estimated OS at 24 months did not reach statistical significance between groups, (94.3% vs 94.6%) p=0.87. The estimated PFS at 24 months for cohort 2 was 88.9%. Efficacy in patients with del17p mutation (cohort 2) remain undefined as results are considered observational due to lack of comparator arm. Grade 3 serious adverse events occurred more frequently in patients treated with BR those treated with zanubrutinib (Brukinsa) (31% vs 20%). Incidence of Grade 3 neutropenia was higher with BR than zanubrutinib (Brukinsa) (22% vs 5%). Grade 1-2 bleeding and cardiac adverse events occurred more frequently with zanubrutinib (Brukinsa) than with BR (41% vs 9%) and (10%

vs 6%), respectively. Several patients who reported major bleeding adverse events were treated with anticoagulants which may confound this safety data. Rates of cardiac arrhythmias with zanubrutinib (Brukinsa) in this study were consistent with those observed in other large, randomized studies of second-generation BTK inhibitors, including zanubrutinib (Brukinsa) and acalabrutinib (Calquence), in B-cell malignancies.

B. Zanubrutinib (Brukinsa) was studied in one phase 1/2 open-label, dose expansion, single-arm trial of B-cell malignancies (BGB-3111-AU-003) in 101 patients with treatment relapsed/refractory CLL or SLL; one phase 2, open-label, single-arm trial (BGB-3111-205) in 91 Chinese patients with relapsed/refractory CLL or SLL; and one phase 3, randomized, open-label, head-to-head study against ibrutinib (ALPINE). The ALPINE study included 652 adult patients with relapsed/refractory CLL or SLL who have tried ≥1 prior systemic therapy consisting of ≥2 cycles of treatment. The median age was 67 years (range, 35 to 90), 73% had unmutated immunoglobulin heavy-chain variable region (IGHV) status, and 23% had a chromosome 17p deletion, TP53 mutation, or both. The median number of previous lines of therapy was 1 (range, 1 to 12). The percentage of patients with an overall response (ORR), as assessed by the independent review committee were higher in the zanubrutinib (Brukinsa) group than in the ibrutinib group (86.2% vs 75.7%). At 24 months, the percentage of patients with progression-free survival, as assessed by the investigators, was 78.4% (95% CI, 73.3 to 82.7) in the zanubrutinib (Brukinsa) group and 65.9% (95% CI, 60.1 to 71.1) in the ibrutinib group. Median progression-free survival was not reached in the zanubrutinib (Brukinsa) group and was 34.2 months (95% CI, 33.3 to not estimable) in the ibrutinib group. Results were consistent in the high-risk population of patients with 17p deletion, TP53 mutation, or both. The percentages of patients who were alive without disease progression at 24 months in the high-risk population were 72.6% (95% CI, 60.3 to 81.7) in the zanubrutinib (Brukinsa) group and 54.6 (95% CI, 40.7 to 66.4) in the ibrutinib group. As of the data-cutoff date in the final analysis, fewer deaths had been reported in the zanubrutinib (Brukinsa) group than in the ibrutinib group (48 and 60). Overall survival was not different in the two groups (hazard ratio for death 0.76; 95% CI, 0.51 to 1.11); longer follow-up is warranted to determine any differences between the treatments with respect to overall survival. The median overall survival had not been reached in either treatment group. Safety profile was comparable between the two treatment arms except, zanubrutinib (Brukinsa) had a higher incidence of Grade ≥3 adverse events compared to ibrutinib: neutropenia (16% vs 13.9%) and hypertension (14.8% vs 11.1%). There was a lower incidence of Grade ≥3 atrial fibrillation/flutter (1.9% vs 3.7%), serious events leading to treatment discontinuation (15.4% vs 22.2%) and events leading to death (10.2% vs 11.1%) in zanubrutinib (Brukinsa) vs ibrutinib treatment groups.

Investigational or Not Medically Necessary Uses

I. The following indications do not have sufficient evidence to support the use of zanubrutinib (Brukinsa) at this time:
   A. Previously untreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma in patients with a del17p mutation

1. The safety and efficacy in patients with del17p mutation was studied in cohort 2 (Group C) of the SEQUOIA trial. Estimated PFS at 24 months was 88.9% (95% CI: 81.3-93.6). Estimated OS at 24 months was 93.6% (95% CI: 87.1-96.9). Due to the open label, single-arm trial design with respect to the cohort 2 population, safety and efficacy remains observational and is undetermined at this time.

B. Diffuse Large B-cell Lymphoma (DLBCL)
C. Follicular Lymphoma (FL)
D. Hairy Cell Leukemia (HCL)
E. Graft-versus Host Disease (GvHD)
F. Marginal Zone Lymphoma (MZL)
    1. For the treatment of MZL, zanubrutinib (Brukinsa) is FDA-approved under the accelerated approval pathway based on ORR and DOR. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Finalized data have not been published on these trials at this time.
    2. Zanubrutinib (Brukinsa) was studied in one Phase 1/2 open-label, dose expansion, single-arm trial of B-cell malignancies including 20 previously treated MZL patients (BGB-3111-AU-003) and one Phase 2, open-label, multicenter, single-arm trial of 68 previously treated patients with MZL who had received at least 1 prior anti-CD20-based regimen (MAGNOLIA). MAGNOLIA study included patients with a median age of 70 years (range: 37 to 85), 38% had extranodal MZL, 38% nodal, 18% splenic and 6% had unknown subtype. The median number of prior systemic therapies was 2 (range: 1 to 6), with 88% of patients having prior rituximab-based chemotherapy, 32% had refractory disease at study entry. ORR was reached in 45 (68.2%) patients while DOR was not reached at the time of data analysis. Twelve-month DOR, PFS, and OS was as 93.0%, 82.5%, and 95.3%, respectively.
    3. The most common adverse events were similar to adverse events seen in clinical trials studying other cancer types and included diarrhea, contusion, constipation, pyrexia, and upper respiratory tract infections. Serious adverse events occurred in 38.2% of patients and included COVID-19 pneumonia, pyrexia, and fall. Four patients discontinued treatment due to adverse events and 29.4% of patients had dose interruption due to adverse events.
    4. Treatment of MZL with zanubrutinib (Brukinsa) remains experimental and investigational. The quality of evidence is considered low due to observational nature of clinical trials (single-arm, open-label study designs) with unknown clinical impact on the overall survival rate, health-related quality of life, or symptom improvement in treated patients. Confirmatory trials are needed to definitively establish benefit and value of this agent in MZL.
    5. NCCN guidelines recommend anti-CD20 based regimens as preferred therapies in second-line and subsequent setting as well as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) ibrutinib, lenalidomide + rituximab, and zanubrutinib with a Category 2A recommendation. Other recommend regimens additionally umbralisib and PI3K inhibitors in patients relapsed/refractory after 2 prior therapies.

G. Indolent Non-Hodgkin Lymphoma (iNHL)
H. MCL monotherapy
    1. For the treatment of MCL, zanubrutinib (Brukinsa) was FDA-approved under the accelerated approval pathway based on overall response rate (ORR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials; however, finalized data has not been published on these trials at this time.
    2. Zanubrutinib (Brukinsa) was studied in one open-label, single-arm, Phase 2 trial (BGB-3111-206), and one Phase 1/2 safety and pharmacokinetic trial (BGB-3111-AU-003) in 118 patients with MCL who had progressed on prior systemic therapy. The primary efficacy outcome was ORR which was 84% in both trials. Secondary efficacy outcomes were complete response (CR), partial response (PR), and duration of response (DOR). The percentage of patients with a CR was 59% and 22% for the Phase 2 trial and Phase 1/2 trial, respectively. The percentage of patients with a PR was 24% and 62% for the Phase 2 trial and Phase 1/2 trial, respectively. Median DOR in months was 19.5 and 18.5 for the Phase 2 trial and Phase 1/2 trial, respectively. Progression-free survival was evaluated in the Phase 2 trial and found 74.6% of patients at 12 months were progression-free.
    3. Treatment of MCL with zanubrutinib (Brukinsa) remains experimental and investigational. The quality of evidence is considered low due to observational nature of clinical trial (single-arm, open-label study design) with unknown clinical impact on the overall survival rate, health-related quality of life, or symptom improvement in treated patients. Confirmatory trials are needed to definitively establish benefit and value of this agent in MCL.
I. MCL first-line therapy
J. MCL combination therapy
K. Richter's Transformation

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

I. Brukinsa [Prescribing Information]. Beigene USA, Inc.: San Mateo, CA. September 2021.
II. Brukinsa [Manufacturer e-dossier]. Beigene USA, Inc.: San Mateo, CA. September 2021.
III. Nasdaq Investors. BeiGene Announces Results of Phase 3 ASPEN Trial of Zanubrutinib Compared to Ibrutinib for the Treatment of Patients with Waldenstrom's Macroglobulinemia. http://ir.beigene.com/news-releases/news-release-details/beigene-announces-results-phase-3-aspen-trial-zanubrutinib?loc=US. Written December 16, 2019. Accessed December 19, 2019.
IV. National Comprehensive Cancer Network. NCCN Clinical Practice Guideline in Oncology. B-cell lymphomas. Version 5.2021. September 22, 2021.

V. National Comprehensive Cancer Network. NCCN Clinical Practice Guideline in Oncology. Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma. Version 1.2022. June 24, 2021.
VI. National Comprehensive Cancer Network. NCCN Clinical Practice Guideline in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 1.2023. August 30, 2022.
VII. Opat S, Tedeschi A, Linton K, et al. The Magnolia Trial: Zanubrutinib, A Next-Generation Bruton Tyrosine Kinase Inhibitor, Demonstrates Safety and Efficacy in Relapsed/Refractory Marginal Zone Lymphoma [published online ahead of print, 2021 Sep 15]. Clin Cancer Res. 2021;clincanres.1704.2021. doi:10.1158/1078-0432.CCR-21-1704
VIII. Tam, CS., et al. "A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study." Blood vol. 136,18 (2020): 2038-2050. doi:10.1182/blood.2020006844
IX. Xu, Wei et al. "Treatment of relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma with the BTK inhibitor zanubrutinib: phase 2, single-arm, multicenter study." Journal of hematology & oncology vol. 13,1 48. 11 May. 2020, doi:10.1186/s13045-020-00884-4
X. Tam CS, Brown JR, Kahl BS, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial [published online ahead of print, 2022 Jul 7]. Lancet Oncol. 2022;S1470-2045(22)00293-5. doi:10.1016/S1470-2045(22)00293-5
XI. Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or Ibrutinib in Relapsed or Refractory Chronic Lymphocytic Leukemia [published online ahead of print, 2022 Dec 13]. N Engl J Med. 2022;10.1056/NEJMoa2211582. doi:10.1056/NEJMoa2211582

Policy Implementation/Update:

Action and Summary of Changes	Date
Removed criterion requiring use of other BTKi before Brukinsa in relapsed/refractory CLL/SLL. Added previously untreated CLL/SLL indication and associated criteria. Added previously untreated CLL/SLL with del17p mutation as E/I. Changed the length of initial approval from three to six months. Updated supporting evidence section.	12/2022
Removed initial criteria and moved MCL indication to experimental or not medically necessary uses section.	01/2022
Added initial criteria for non-FDA approved indication of CLL/SLL and updated supporting evidence. Added Richter's Transformation in the E/I section.	12/2021
Added expanded indication of Waldenström's macroglobulinemia (WM) in the initial evaluation criteria. Updated supporting evidence section to include clinical trial information for WM. Added supporting evidence for the expanded indication of marginal zone lymphoma (MZL) in investigational uses section.	11/2021
Policy created	02/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP293

Description

Zilucoplan (Zilbrysq) a targeted C5 complement inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
zilucoplan (Zilbrysq)	Myasthenia Gravis	16.6 mg/0.416 mL	11.648 mL/28 days
		23 mg/ 0.574 mL	16.072 mL/28 days
		32.4 mg/ 0.81 mL	22.68 mL/28 days

Initial Evaluation

I. **Zilucoplan (Zilbrysq)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a specialist (e.g., neurologist or rheumatologist); **AND**
   C. Medication will not be used in combination with maintenance immunoglobulin therapy (IVIG), rituximab, or another biologic for gMG [i.e., eculizumab (Soliris), ravulizumab (Ultomiris), efgartigimod alfa (Vyvgart), rozanolixizumab (Rystiggo)]
   D. A diagnosis of **generalized myasthenia gravis (gMG)** when the following are met:
      1. Provider attestation that the member is acetylcholine receptor antibody positive (AChR-AB+); **AND**
      2. Provider attestation that the member has Myasthenia Gravis Foundation of America (MGFA) Clinical Classification class II to IV disease (i.e., not defined as ocular myasthenia gravis and not intubated); **AND**
      3. Member has a baseline MG-activities of daily living (MG-ADL) score ≥6; **AND**
   E. Member has had an inadequate response (e.g., unable to maintain baseline MG-ADL score) after a minimum of one-year trial of each of the following therapies, unless both were not tolerated or contraindicated:
      1. Acetylcholinesterase inhibitor (e.g., pyridostigmine); **AND**
      2. An oral immunosuppressant (e.g., azathioprine, cyclosporine, mycophenolate, low dose daily glucocorticoids); **OR**
   F. Member required chronic treatment with plasmapheresis or plasma exchange or intravenous immunoglobulin (IVIG) in addition to immunosuppressant therapy; **AND**
   G. Member will be continuing on standard of care therapies (e.g., pyridostigmine, azathioprine, low dose daily glucocorticoids) unless all are contraindicated or not tolerated

II. Zilucoplan (Zilbrysq) is considered investigational when used for all other conditions, including but not limited to:
   A. Ocular Myasthenia Gravis
   B. Myasthenia Gravis MUSK antibody positive or other antibodies that are not AChR
   C. Pediatric Myasthenia Gravis
   D. Postural Orthostatic Tachycardia Syndrome
   E. Primary Immune Thrombocytopenia
   F. Paroxysmal Nocturnal Hemoglobinuria

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Provider attests that the member continues to have a clinical response to zilucoplan (Zilbrysq) (i.e., an improvement in the MG-ADL score, a reduction/elimination of oral steroids/immunosuppressants required, etc.); **AND**
IV. Medication will not be used in combination with maintenance immunoglobulin therapy (IVIG), rixtuximab, or another biologic for gMG [i.e., eculizumab (Soliris), ravulizumab (Ultomiris), efgartigimod alfa (Vyvgart), rozanolixizumab (Rystiggo)]

Supporting Evidence

I. Zilucoplan (Zilbrysq) is FDA approved to treat adult patients with generalized myasthenia gravis (gMG) that are anti-acetylcholine receptor antibody positive (AChR-AB+). Use in individuals under the age of 18 years as well as use in other antibody positive patients has not been determined to be safe and effective at this time.
II. Due to the complexity of diagnosing and treating gMG, zilucoplan (Zilbrysq) must be prescribed by, or consultation with, a specialist in neurology or rheumatology.
III. Myasthenia gravis is a chronic, autoimmune, neuromuscular disease characterized by fluctuating motor weakness involving the ocular, spinal column, limb and/or respiratory muscles. The weakness is due to an antibody-mediated, immunologic attack directed at the postsynaptic membrane of the neuromuscular junction (acetylcholine receptors [AChR] or receptor associated proteins, such as MUSK) led by an IgG immune response. This causes common symptoms such as drooping eyelids (ptosis) and double vision (diplopia), muscle weakness and fatigue, trouble swallowing or pronouncing words, and facial muscle involvement causing a mask-like appearance or sneer.
IV. AChR are the most common receptor affected; about 85% of patients will test positive for AchR antibodies, which is considered a positive indicator of a MG diagnosis. Those who do not test positive for AchR, may then test positive for a different receptor protein, such as muscle-specific tyrosine kinase (MuSK) or LR4 antibody. AchR antibody (AchR-AB) negative patients do not tend to respond as well to regular standards of care as the AB positive patients do and tend to respond better to rituximab (Inflectra) instead.

V. Additionally, there are two clinical forms of MG: ocular and generalized. Although the majority of patients present with a vision symptom as the first indicator of MG, roughly 15% of patients remain as ocular MG, while the rest become generalized MG. Those with ocular MG are less likely to be AchR-AB positive and have mixed response to traditional therapies usually favoring eye patches or eye "crutches" to assist with drooping eyelids, and in severe cases, surgery.

VI. Clinical presentation of MG is staged by ocular versus generalized and the severity of their symptoms. Stage I is ocular only and Stage V is those patients who require intubation; Stages II-IV encompass those patients in between as mild to moderate and the systems involved. MG are further assessed by two common scoring systems: the Quantitative Myasthenia Gravis (QMG) and the MG activity of daily living (MG-ADL). Both are quality of life scales assessing muscle strength and weakness, higher scores on each scale indicate more severe disease. QMG is a 13-item scale with a possible worst score of 39 and MG-ADL is an 8-item scale with a possible worst score of 24. Based on clinical data and physician input, a three-point change is clinically meaningful in QMG for moderate-severe presentation and a two-point change for milder presentation; a two-point change is clinically meaningful in MG-ADL for mild-moderate, there is not an agreement on severe patients in the MG-ADL scale.

VII. Currently there is no cure for MG, patients tend to reach their peak in symptoms and severity within the first three years of diagnosis and then stabilize or move into remission. Available treatments control symptoms and prevent relapses allowing patients to live a relatively high quality of life with a normal life expectancy. Treatment options include symptomatic treatment (e.g., acetylcholinesterase inhibitors [e.g., pyridostigmine]), corticosteroids, long-term immunosuppressive therapy (e.g., azathioprine, cyclosporine, methotrexate), plasma exchange, and rapid immunomodulating treatments (e.g., immune globulin IV). Thymectomy is also an option and according to the Internal Consensus Guidelines on MG 2020, thymectomy should be considered early in the disease for those under 50 years of age with generalized MG or those who fail to respond to an adequate trial of immunotherapy and have stable MG amenable to surgery (i.e., no current flares, on stable dose of medications without changes being made). The only biologic treatment currently included in these same guidelines is eculizumab (Soliris), also a C5 inhibitor, which is recommended in the treatment of severe, refractory, AchR-AB+ gMG. Internal Consensus Guidelines define refractory disease as an unchanged or worse MG-ADL/QMG after corticosteroids and at least two other immunosuppressant agents. The presence of persistent symptoms or side effects that limit functioning after treatment used at the maximum dose the patient is able to tolerate for an adequate duration (typically 12 weeks).

VIII. Pyridostigmine is recommended as initial therapy and unless not tolerated. Patients should remain on this therapy lifelong as a standard of care. The ability to discontinue pyridostigmine can be indicative of meeting therapy goals and may guide tapering of other drugs. For patients that continue to experience bothersome symptoms, next line agents include nonsteroidal immunosuppressants (NISTs) such as azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. NIST can be used in combination with a corticosteroid (prednisone) for flares or more rapid deceleration of exacerbation/crisis. Myasthenia crisis can occur from concurrent infection, surgery, pregnancy, and certain medication classes. Mild flares may simply respond to changes in standard of care doses or frequency, such as increasing pyridostigmine, or beginning a course of prednisone. More severe cases where patients are experiencing increased dysphagia or dyspnea, initiation of intravenous immune globulin (IVIG) or plasmapheresis, are used to return to clinical baseline.

IX. The safety and efficacy of zilucoplan (Zilbrysq) was evaluated in RAISE, a Phase 3 multicenter, randomized, double-blind, placebo-controlled study. The trial evaluated 174 AChR-Ab+ adult patients with gMG between Stage II-IV. All patients had a MG-ADL score ≥6 and were randomized 1:1 to receive either placebo (n=88) or 0.3mg/kg zilucoplan (Zilbrysq, n=86) SC daily over 12 weeks. Patients were required to remain on standard-of-care therapies during the study that they were on preceding the trial start (i.e., pyridostigmine, NISTs) so long as there was not a change in dose or frequency or an anticipated need to change during the 12-week study. Approximately 85% of patients were on pyridostigmine, 63% steroids, and 51% NISTs. Data was considered missing if rescue therapy for a crisis or relapse was required. MG-ADL response was the primary endpoint at the end of week 12.

X. A statistically significant difference favoring zilucoplan (Zilbrysq) over placebo was seen at the end of the 12-week trial. Patients taking zilucoplan (Zilbrysq) had a change of 4.39 points versus 2.30 in placebo of the MG-ADL score [-2.09 (-3.24, -0.95); *p <0.001*]. Secondary endpoints looked at additional standard improvement/severity scales such as response in QMG, MGC, and MG-QoL 15r scores. These also met a statistically different response in zilucoplan (Zilbrysq) versus placebo. A total of 200 patients enrolled into the ongoing extension trial (RAISE-XT). RAISE-XT was primarily a safety extension trial, but secondary endpoints continued to monitor the endpoints of RAISE. These endpoints were maintained or improved at the interim data analysis at week 90. There were no new safety signals at week 90.

XI. There are currently four other biologics approved in the treatment of MG; two complement factors: eculizumab (Soliris) and raculizumab (Ultomiris) and two neonatal Fc receptor (FcRn) inhibitors: efgartigimod (Vyvgart) and rozanolixizumab (Rystiggo). The Internal Consensus Guidelines on Myasthenia Gravis 2020 recommend eculizumab (Soliris) in refractory MG after failure of IVIG, plasmapheresis, and immunosuppressive agents. The exclusion criteria of all four of these trials did not allow concurrent use of each other or IVIG, plasmapheresis, or rituximab within at least four weeks of the trial onset. The combination use of any of these therapies would be considered experimental.

Investigational or Not Medically Necessary Uses

I. Zilucoplan (Zilbrysq) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Ocular Myasthenia Gravis
   B. Myasthenia Gravis MUSK antibody positive or other antibodies that are not AChR
   C. Pediatric Myasthenia Gravis
   D. Postural Orthostatic Tachycardia Syndrome
   E. Primary Immune Thrombocytopenia
   F. Paroxysmal Nocturnal Hemoglobinuria

Appendix

I. **MGFA Clinical Classification:**

Class	Distribution and Severity	
1	Any ocular muscle weakness, all other muscle strength is normal	
2	Mild, generalized	• 2a: Mainly limp, axial muscles

		• 2b: mainly oropharyngeal/respiratory muscles
3	Moderate, generalized	• 3a: Mainly limp, axial muscles
		• 3B: Mainly oropharyngeal/respiratory muscles
4	Severe, generalized	• 4a: Mainly limp, axial muscles
		• 4B: Mainly oropharyngeal/respiratory muscles
5	Intubation	

II. **MG-ADL Score:**

	Score=0	Score=1	Score=2	Score=3	Your Score
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal speech, but can be understood	Difficult to understand speech	
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilatory dependence	
Brushing teeth or hair	Normal	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
Arising from chair	Normal	Mild, sometimes uses arms	Moderate, always uses arms,	Severe, requires assistance	
Double vision	Normal	Occurs, but not daily	Daily, but not constant	Constant	
Eyelid droop	Normal	Occurs, but not daily	Daily, but not constant	Constant	
				Total Score=	

References

1. Zilbrysq [Prescribing Information]. UCB, Inc. Smyrna, GA. October 2023.
2. Narayanaswami P, Sanders DB, Wolfe G, et al. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update. *Neurology*. 2021 Jan 19;96(3):114-122.

3. Howard JF Jr, Bresch S, Genge A, et al. Safety and efficacy of zilucoplan in patients with generalised myasthenia gravis (RAISE): a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Neurol*. 2023;22(5):395-406. doi:10.1016/S1474-4422(23)00080-7
4. Zilucoplan – Long-term data in adult patients with generalized myasthenia gravis (RAISE-XT) MED-GL--2202942

Related Policies

Currently there are no related pharmacy policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2024

Policy Type: PA/SP Pharmacy Coverage Policy: UMP285

Description

Zuranolone (Zurzuvae) is an orally administered neuroactive steroid $GABA_A$ receptor positive allosteric modulator.

Length of Authorization

I. Initial: One time fill
- Renewal: No renewal

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
zuranolone (Zurzuvae)	Postpartum depression	20mg capsule	28 capsules/14 days
		25mg capsule	
		30mg capsule	14 capsules/14 days

Initial Evaluation

I. **Zuranolone (Zurzuvae)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. A diagnosis of **Postpartum Depression** when the following are met:
      1. Member has severe depressive symptoms as demonstrated by an objective measurement scale score consistent with severe designation (e.g., HAMD-17, MADRS, etc.); **AND**
      2. Onset of depressive symptoms occurred during the third trimester OR within the first four weeks after delivery; **AND**
      3. Member has discontinued breastfeeding; **OR**
         i. Member has agreed to temporarily hold breastfeeding for course of therapy and one week following; **AND**
      4. Treatment with at least one SSRI (e.g., citalopram [Celexa], escitalopram [Lexapro], fluoxetine [Prozac], sertraline [Zoloft], etc.) OR SNRI (e.g., duloxetine [Cymbalta], desvenlafaxine succinate [Pristiq], venlafaxine [Effexor], etc.) has been ineffective, contraindicated, or not tolerated.

II. Zuranolone (Zurzuvae) is considered <u>not medically necessary</u> when criteria above are not met and/or when used for:
   A. Major Depressive Disorder (MDD)

III. Zuranolone (Zurzuvae) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Use in the pediatric population
   B. Depressive episodes in bipolar II disorder

C. Episodic treatment of MDD and/or PPD
D. Treatment resistant depression
E. Other psychiatric disorders

Supporting Evidence

I. The safety and efficacy of zuranolone (Zurzuvae) was evaluated in a total of five phase 3 randomized, double-blind, placebo-controlled trials that made up two clinical programs. The LANDSCAPE clinical program (MOUNTAIN, WATERFALL, CORAL) focused on major depressive disorder (MDD), while the NEST clinical program (ROBIN, SKYLARK) focused on postpartum depression (PPD). As of August 2023, the FDA has only approved zuranolone (Zurzuvae) for treatment of PPD.

II. Zuranolone (Zurzuvae) was studied in adult patients aged 18 and older and has not been evaluated for safety and/or efficacy in pediatric patients.

III. **PPD**

- The SKYLARK trial was a randomized, double-blind, placebo-controlled trial that evaluated the safety and efficacy of a single 14-day course of zuranolone 50mg compared to placebo in adult women with severe postpartum depression, as evidenced by a baseline HAMD-17 score of at least 26, who had onset of depressive symptoms during the third trimester or first four weeks after delivery. The primary efficacy endpoint was change from baseline in HAMD-17 score at day 15, which was met (LS means, -15.6 (0.80) vs. -11.6 (0.89), p=0.007).
- Patients who were actively breastfeeding were excluded from participation in the clinical trials. To be included, patients were required to have either completely ceased breastfeeding or agreed not to provide breastmilk to their infant(s) from just prior to receiving the study drug on day one of the trial period until seven days after the last dose of the study drug. Data from a Phase 1, single-center, open-label study conducted in healthy, lactating adult females that was designed to evaluate the pharmacokinetics and safety of zuranolone (Zurzuvae) demonstrated that the estimated relative infant dose (RID), calculated as the infant dose divided by the maternal dose, was 0.357% on day 5 and the estimated daily infant dose was 0.00124 mg/kg/day. The estimated mean RID was consistent with a low fraction of unbound zuranolone (Zurzuvae) in plasma (≤0.52%). Maternal milk production decreased by 8.3% (41.2 [140.11] mL) in volume collected at day five compared to baseline. Investigators noted that the interpretation of the effect of zuranolone (Zurzuvae) on milk production is limited due to variability inter-patient milk production at baseline, lack of placebo control, and the small sample size (N=15).

IV. The majority of TEAEs observed throughout the clinical program were considered mild or moderate in severity, with serious adverse events (SEAs) occurring in <2% of zuranolone (Zurzuvae) treated patients. Across the clinical program, there was no observed increase in incidence of suicidal ideation. The most common TEAEs (>5%) include headache, somnolence, dizziness, nausea, sedation, fatigue, and diarrhea.

V. For treatment of PPD, the American Academy of Family Physicians (AAFP) and National Institute for Health (NIH) recommend psychotherapy alone for mild-to-moderate PPD and pharmacologic

treatment with select SSRIs and SNRIs for moderate-to-severe PPD. The antidepressants recommended for PPD include citalopram, escitalopram, fluoxetine, paroxetine, sertraline, desvenlafaxine, duloxetine, venlafaxine, and bupropion.

- Brexanolone (Zulresso) is an IV-administered neuroactive steroid GABAA receptor positive allosteric modulator that FDA-approved in the setting of PPD. This 60-hour continuous infusion is currently recommended by UpToDate for patients with severe PPD who prioritize fast onset of action and should be followed by a guideline-recommended SSRI or SNRI as maintenance therapy. As of July 2023, guidelines have not been updated to include brexanolone (Zulresso) or zuranolone (Zurzuvae), so there is minimal insight as to the appropriate use of zuranolone (Zurzuvae) following prior treatment with brexanolone (Zulresso) in the current or previous episode of PPD.

Investigational or Not Medically Necessary Uses

I. Zuranolone (Zurzuvae) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Major Depressive Disorder
      i. The safety and efficacy of zuranolone (Zurzuvae) in the setting of adult patients with severe MDD was evaluated in the LANDSCAPE clinical program, which is made up of three clinical trials: the MOUNTAIN, WATERFALL, and CORAL clinical trials. The MOUNTAIN and WATERFALL clinical trials evaluated zuranolone (Zuzuvae) as either monotherapy or adjunct to antidepressant therapy, as long as they were established on therapy on a stable antidepressant dose for at least 60 days prior to baseline. The CORAL clinical trial evaluated zuranolone (Zurzuvae) when co-initiated with standard of care antidepressant therapy. The primary endpoint in all trials was the change from baseline (CFB) in the baseline Hamilton Depression Rating Scale (HAMD-17) at day 15, with the exception of the CORAL trail which evaluated this endpoint at day 3. The primary endpoint was statistically significant in favor of zuranolone (Zurzuvae) in the WATERFALL (least square mean [LSM] change, -14.1 [SE=0.5] vs. -12.3 [SE=0.5], p=0.01) and CORAL (LSM change, -8.9 vs. -7.0, p=0.004) clinical trials, but not the MOUNTAIN clinical trial.
      ii. Although the results of the LANDSCAPE clinical program demonstrated statistically significant change from baseline in HAMD-17 scores, this did not correlate to a clinically meaningful change compared to placebo, defined as a difference of 4 or more points on the HAMD-17 scale. Due to a lack of clinically meaningful impact on depressive symptoms compared to placebo, the value of zuranolone (Zurzuvae) as compared to standard of care antidepressant therapy remains undefined at this time.
      iii. On August 4, 2023, the FDA released a complete response letter (CRL) for the new drug application (NDA) for zuranolone (Zurzuvae) for the MDD indication. The CRL stated that the application did not provide substantial evidence of effectiveness to support approval of zuranolone (Zurzuvae) for the treatment of MDD, and that an additional study or studies will be needed. Given variable primary endpoint results

and lack of clinically meaningful impact on depressive symptoms compared to placebo throughout the clinical program, treatment of MDD with zuranolone (Zurzuvae) is not medically necessary.

B. Use in the pediatric population
C. Depressive episodes in bipolar II disorder
D. Episodic treatment of MDD and/or PPD
    i. As of August 2023, zuranolone (Zurzuvae) has only been approved as a single treatment course for treatment of PPD. Zuranolone (Zurzuvae) is also being evaluated in an ongoing, open-label, phase 3, observational trial evaluating the safety and tolerability of an initial course of zuranolone (Zurzuvae) 30mg or 50mg and the need for repeat courses in adults with MDD for up to 1 year. At the primary cutoff point in November 2021, zuranolone (Zurzuvae) appeared to generally well tolerated, with reported treatment emergent adverse events (TEAEs) consistent with existing clinical trial data. Most patients in the zuranolone (Zurzuvae) 50mg cohort received one or two total treatment courses during the study period, up to one year (79.5% [116/146]), with median time to first repeat treatment course of 249 days. There are no studies currently underway to evaluate episodic treatment in PPD.
E. Treatment resistant depression
F. Other psychiatric disorders

References

1. Hirst KP, Moutier CY. Postpartum Major Depression. Am Fam Physician. 2010;82(8):926-933.
2. Guille C, Newman R, Fryml LD, et al. Management of Postpartum Depression. J Midwifery Womens Health. 2013; 58(6): 643–653. doi:10.1111/jmwh.12104.
3. American Psychological Association. (2019). Clinical practice guideline for the treatment of depression across three age cohorts. Retrieved from https://www.apa.org/depression-guideline
4. Clayton AH, Lasser R, Nandy I, et al. Zuranolone in Major Depressive Disorder: Results from MOUNTAIN – A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial. J Clin Psychiatry 2023;84(2):22m14445.
5. Clayton AH, Lasser R, Parikh SV, et al. Zuranolone for the Treatment of Adults with Major Depressive Disorder: A Randomized, Placebo-Controlled Phase 3 Trial. AJP in Advance (doi: 10.1176/appi.ajp.20220459).
6. Deligiannidis KM, Meltzer-Broday S, Gunduz-Bruce H, et al. Effect of Zuranolone vs Placebo in Postpartum Depression: A Randomized Clinical Trial. JAMA Psychiatry. 2021;78(9):951-959. doi:10.1001/jamapsychiatry.2021.1559.
7. Viguera A, et al. Severe postpartum unipolar major depression: Choosing treatment. UpToDate. Last updated March, 14, 2023. Accessed from: https://www.uptodate.com/contents/severe-postpartum-unipolar-major-depression-choosing-treatment?search=postpartum%20depression%20treatment&source=search_result&selectedTitle=2~145&usage_type=default&display_rank=2.,

Related Policies

Policy Name	Disease state
esketamine (Spravato™) Policy	Treatment resistant depression (TRD) and Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	08/2023

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U.S. Department of Health and Human Services
200 Independence Avenue, SW Room 509F, HHH Building
Washington, D.C. 20201

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โปรดทราบ: หากคุณพูดภาษาไทย คุณสามารถใช้บริการช่วยเหลือด้านภาษาได้ฟรี โทร 1-888-361-1611 (TRS: 711)

FA'AUTAGIA: Afai e te tautala i le gagana Samoa, o loo avanoa fesoasoani tau gagana mo oe e le totogia. Vala'au i le 1-888-361-1611 (TRS: 711)

IPANGAG: Nu agsasaoka iti Ilocano, sidadaan ti tulong iti lengguahe para kenka nga awan bayadna. Umawag iti 1-888-361-1611 (TRS: 711)

UWAGA: Dla osób mówiących po polsku dostępna jest bezpłatna pomoc językowa. Zadzwoń: 1-888-361-1611 (obsługa TRS: 711)